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XIV. Effect of Heat and pH on the Precipitin Reaction and Reagin Neutralizing Capacity of the Castor Bean Allergen, CB-1C

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MAXIMUM industrial utilization of castor bean pomace has been prevented because the allergen contained in castor beans has unusually potent sensitizing capacity for those exposed to the dust, and because this allergen provokes severe asthma in hypersensitive individuals. The problem of industrial inactivation of the allergen has been complicated by the fact that the allergen is stable to heat treatment which destroys the potent toxalbumin, ricin.

The first recorded case of hypersensitivity to castor beans was described in 1914 by Alilaire who attributed the allergenic activity to ricin.[1] The first recorded case of occupational castor bean sensitivity was that of a chemist working at the United States Department of Agriculture described by Bernton.[2] Since then, many cases of hypersensitivity to castor beans have been reported. Figley and Elrod[3] described the first endemic asthma involving thirty cases within a one-mile radius of a castor bean processing plant. Ordman[4] described an outbreak of asthma in South Africa affecting

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Previous paper in this series, "The Chemistry of Allergens XIII. Ion-Exchange Fractionation of the Cottonseed Allergen and Immunological Properties of the Products" by Joseph R. Spies, Dorris C. Chambers and E. J. Coulson. *Archives of Biochemistry and Biophysics,* 84:286 (Oct.) 1959.

over two hundred persons caused by dust from a castor oil processing plant. Castor bean allergy due to contamination of burlap bags and of green coffee also has been reported.[5-7] The literature on this subject is reviewed by Ordman and need not be repeated here.

The isolation and properties of the principal allergen of castor beans, CB-1A or CB-1C (see material used) have been described in previous papers from this laboratory.[8-13] CB-1C is a polysaccharide protein belonging to the natural proteose classification which represented 1.8 per cent of ether defatted domestic castor beans and 0.33 per cent of commercial pomace by isolation. The allergenic and antigenic specificities of CB-1C are attributed to the protein component. CB-1C is water soluble, stable in boiling water, precipitated by 75 per cent ethanol and soluble in basic lead acetate solution. CB-1C is composed of known amino acids with relatively high arginine and glutamic acid contents and no tryptophan. CB-1C contains no ricin and is nontoxic.

The object of this paper is to describe the effect of heating CB-1C in buffered solutions at pH values of 4, 5, 6, 7, 8, 9, and 10 at temperatures of 100, 115, and 130° C for various periods of time: (1) on the precipitating capacity with castor bean allergen rabbit antiserum, and (2) on the *in vivo* reagin neutralizing capacity by a passive transfer method with serum from a castor bean sensitive person.

MATERIAL USED

Castor Bean Allergen, CB-1C.—CB-1C was isolated from commercial Brazilian castor bean pomace by the "1C" procedure.[13] The nitrogen content was 13.6 per cent, air-dried basis. The difference between CB-1A and CB-1C is in the method of removal of lead in the isolation procedure. Lead was removed with sodium carbonate in the preparation of CB-1A and with hydrogen sulfide in the preparation of CB-1C. The two preparations were chemically and immunologically indistinguishable.

Castor Bean Allergen, CB-13E.—Some unimportant polysaccharide and some denatured protein were eliminated from CB-1A by precipitation with picric acid and recovery of active fraction CB-13 by removal of the picric acid from the precipitate. CB-13E was prepared by dialysis of CB-13 by essentially the same procedure used to obtain the corresponding fraction CS-13E from the cottonseed allergen, CS-1A.[14] Eleven grams of CB-13 were obtained from 21.1 g of CB-1A. Three and four tenths grams of CB-13E, and 4.9 g of combined dialysates were obtained by dialysis of 10.8 g of CB-13. CB-13E contained 17.95 per cent nitrogen and 2.48 per cent polysaccharidic carbohydrate (ash-water-free basis).

Rabbit Antiserum.—Rabbits were immunized to CB-13E by a series of inoculations of antigen in Freund's complete adjuvant[15-17] followed by a series of intraperitoneal injections of antigen in saline according to the following schedule: Twelve rabbits were given four weekly subcutaneous injections of 4 mg of CB-13E contained in 0.5 ml of Freund's adjuvant.

Serum prepared from blood drawn two weeks after the fourth inoculation showed only a trace of precipitin. Accordingly, the animals were given two more weekly inoculations of CB-13E in the adjuvant followed in one week by a series of four daily intraperitoneal injections of 0.5 ml. of 2 per cent CB-13E in saline solution. Serum prepared one week later showed copious precipitates with the antigen. After an interval of four days, the rabbits were again treated with four daily intraperitioneal injections of antigen in saline and were bled one week later. This latter schedule was repeated for a total of five bleedings. The quantitative precipitin content of this serum will be presented in another report.

TABLE I. STABILITY OF BUFFER SOLUTIONS TO HEAT

pH of Buffer	Composition	pH After Heating Thirty-Two Hours[1]	
		100°C	150°C
4	Acetate	—	4.0
5	Acetate	5.00	4.91
6	Acetate	5.96	5.80
7	Phosphate	6.94	7.00
8	Phosphate-borate	8.15	7.84
9	Phosphate-borate	8.85	8.92
10	Glycine-sodium hydroxide	9.84	9.60

[1] Heated in sealed, Pyrex glass tubes.

Reaginic Serum.—Approximately 250 ml of serum was obtained from a castor bean sensitive person, E. McL. All of the tests were conducted with the same lot of serum which was stored at 5° C. Sufficient serum for two weeks testing was transferred to a small sterile vial because it was observed that repeated removals of serum from a vial over a period of four weeks caused noticeable decrease in reagin content.

Buffered Solutions of CB-1C.—One tenth molar buffer solutions were used to prepare 1 per cent solutions of CB-1C. The composition of the buffers and their stabilities (without CB-1C) when heated in sealed Pyrex tubes at 100° and 150° are shown in Table I.

Recipients for Passive Transfer Tests.—Recipients for the passive transfer tests were volunteer castor-bean nonreactors selected from among inmates of the District of Columbia Workhouse, Occoquan, Virginia. The recipients were free from antihistamine medication.

EXPERIMENTAL

Heating CB-1C Solutions.—Three ml of CB-1C in buffer solution was placed in a 15 x 120 mm heavy wall Pyrex tube which was sealed by flame. Sealed tubes were placed in 15 ml metal centrifuge cups which were already at the temperature of the test. The metal cups were placed upright in an aluminum block 7 cm high by 14 cm in diameter which was bored to hold eight tubes and a thermometer, the block being at the test tempera-

ture at the start. Heating was carried out in an oven at constant temperature ± 1° C.

Preparation of Heated Solutions for Precipitin Tests.—One ml of heated CB-1C solutions was titrated to determine the amount of dilute hydrochloric acid or sodium hydroxide required to adjust the pH to between 6.5 and 7.5. The calculated amount of acid or alkali was then added to the remaining 2 ml and the volume was adjusted to 4.0 ml with buffered saline diluting fluid, giving a dilution of 1/200 (Solution A). Other desired dilutions were made with buffered saline solution, pH 7.0, for the precipitin tests.

Precipitin Test.—Fifteen hundredths ml of CB-13E rabbit antiserum in a 5 x 45 mm tube was mixed with 0.15 ml of CB-1C solution and incubated for thirty minutes at 37° C. The tubes were then placed in the refrigerator and the amount of precipitate read visually after forty-eight hours. Average of the precipitin test with unheated CB-1C diluted 1:200, $1:10^3$, $1:10^4$, $1:10^5$ against rabbit anti-CB-13E serum were 2+, 3+, 2+ and 1+, respectively. Control tests with unheated CB-1C in the buffer solutions against normal rabbit serum were negative.

Preparation of Solutions for Passive Transfer Tests.—Solution A, remaining after the precipitin test, was sterilized by filtration through a Pyrex bacterial filter into sterile 15 ml vials.

Reagin Neutralization Method.—Sensitized sites were located as follows: sites 1 and 2, anterior aspect of the forearm, 3½ and 1½ inches below the bend of the elbow, respectively; sites 3 and 4, upper aspect of the biceps, 2½ and 4½ inches above the bend of the elbow, respectively. Sites were used in pairs of 1 and 2, and 3 and 4 on the same arm so that 4 pairs were available, 1 pair being used for each complete test.

The reagin neutralization method is described on a day-by-day basis, four days being required for the test.

First Day, Sensitization.—Each recipient, in groups of approximately twenty-five, was sensitized by intracutaneous injection of 0.05 ml of E. McL. serum into site 1 when pair 1 and 2 was used or site 3 when pair 3 and 4 was used.

Second Day, Challenge of Site.—Site 1 or 3 was injected intracutaneously with 0.025 ml of unheated CB-1C of known concentration or with 0.025 ml of the heated CB-1C solution. The size of the wheal produced in thirty minutes was measured.

Third Day, Resensitization.—Each recipient was sensitized by intracutaneous injection of 0.05 ml of E. McL. serum in site 2 or 4 of the

same arm used on the first day of the test. This site was a positive control in the test for reagin neutralization on the fourth day. This site was not sensitized on the first day because of the possibility of reagin neutralization by migration of allergen from injected site, 1 or 3.

Fourth Day, Test for Reagin Neutralization.—Each recipient was injected subcutaneously with 1.0 ml of sterile, unheated saline solution containing 1 mg of CB-1C on the outer aspect of the upper arm opposite that having the sensitized sites. This method of challenge eliminated need for a control test. Inasmuch as the sites were challenged via the body fluids, there was no trauma of sites by needle injection or irritation by solvent. The challenge dose was large enough to produce reaction with all residual reagins under the condition of the tests.

Reagin Neutralization with Unheated CB-1C.—The threshold amount of unheated CB-1C required to neutralize reagins in injected sites 1 or 3 was determined in a test using two-fold serial dilutions of CB-1C ranging from 0.13 to 512 millimicrogram/0.025 ml. A shorter range of concentrations, usually from 4 to 128 millimicrograms of unheated CB-1C/0.025 ml was used concurrently in each series of tests on the heated CB-1C solutions in order to be certain that the threshold value did not change appreciably.

Reagin Neutralization with Heated CB-1C.—The reagin neutralizing capacities of the heated CB-1C solutions were determined by injecting sites 1 or 3 on the second day of the test with 0.025 ml of sterilized Solution A which contained 125,000 millimicrograms of CB-1C.

RESULTS AND DISCUSSIONS

Results of the effect of heating solutions of CB-1C at 100, 115, and 130° C at pH values of 4, 5, 6, 7, 8, 9, and 10 from one to thirty-two hours on the precipitin reaction and on the reagin neutralizing capacity are shown in Table II. The times required to reduce the precipitating capacity from an average of 3+ at 1:1000 to a ± or doubtful value at 1:1000 dilution are shown in Column A and the times required to completely destroy precipitating capacity at 1:1000 are shown in Column B. It is evident that there is a considerable period of time during which doubtful precipitin values are obtained. For example, at 130°, pH 4, the precipitating capacity was reduced to a ± value in less than one hour, while eight hours was required to give a clear-cut negative value.

The destruction of reagin neutralizing capacity of CB-1C is shown in Column C where the time required to reduce this property to less than 0.026 per cent of its original value is recorded. A typical determination of the reagin neutralizing capacity of unheated CB-1C is shown in Table III where results with two-fold serial dilutions of CB-1C ranging from 0.13 millimicrogram to 512 millimicrograms are shown. Of nine deter-

minations over the critical range, the neutralizing amounts of unheated CB-1C were: 32 millimicrograms, six times; 16 millimicrograms, twice; and 8 millimicrograms, once. Therefore, 32 millimicrograms of unheated CB-1C was chosen as the quantity required to neutralize reagins in 0.05

TABLE II. TIME OF HEATING REQUIRED TO DESTROY THE PRECIPITIN REACTION AND REAGIN NEUTRALIZING CAPACITY OF CB-1C

Time of Heating, in Hours

pH	Temperature °C	Precipitating Capacity		Reagin Neutralizing Capacity
		A	B	C
4	100	>32	>32	>32
	115	8	16	>32
	130	<1	8	4
5	100	>32	>32	>32
	115	8	>32	>32
	130	<1	8	4
6	100	>32	>32	>32
	115	4	8	>32
	130	4	16	4
7	100	8	16	>32
	115	2	4	32
	130	<1	2	<1
8	100	2	16	>32
	115	2	4	32
	130	<1	<1	<1
9	100	4	8	4
	115	<1	2	<1
	130	<1	<1	<1
10	100	—	2	8
	115	<1	2	<1
	130	<1	<1	—

ml of serum under the conditions of the test. Since 0.025 ml of heated CB-1C solution contained 125,000 millimicrograms, failure to neutralize reagins by a heated CB-1C solution indicated retention of less than 0.026 per cent of its original reagin neutralizing capacity.

Comparison of results in Columns A and B show that there is a considerable period of time during which ± or doubtful precipitin values are obtained before clear-cut destruction is obtained. Similarly, positive passive transfer reactions were obtained in injected sites even when the reagin neutralizing capacities were reduced to less than 0.026 per cent. This range of allergen degradation where positive direct passive transfer reactions are obtained, but where insignificant reagin neutralization occurs, may be related to that range of precipitating-antigen destruction where ± reactions are obtained. It is recognized that shocking response may be provoked by allergen which is too far degraded to neutralize reagins. It has been previously observed that in destruction of antigenic properties of acid treated cottonseed allergenic fraction CS-56 that 97 per cent of its anaphylactic sensitizing capacity was lost when only 66 per cent of its shocking capacity was destroyed.[18] The relationships of sensitizing capacity and shocking capacity of partially degraded castor bean allergen will

require further study. It seems certain that a criterion indicating loss of shocking capacity would also indicate inability to sensitize, at least for components having the same specificities as found in the original castor beans. A possibility that must be borne in mind in consideration of this problem is that of the sensitization to degradation product having a new and different specificity than found in the original castor beans.

TABLE III. REAGIN NEUTRALIZING CAPACITY OF UNHEATED CB-1C

Challenge[1] Milli-micrograms CB-1C/0.025 ml.	Size of Wheal in Thirty Minutes[1,2]	Test for Neutralization Reaction in Sixty Minutes[2,3]	
		Site No.	
	Site No. 1 or 3	1 or 3	2 or 4[4]
0.13	±	3+	4+
.25	0	3+	3+
.50	0	4+	4+
1.0	2+	3+	2+
2.0	2+	3+	3+
4.0	2+	3+	4+
8.0	2+	2+	2+
16	2+	0	3+
32	3+	0	3+
64	3+	0	3+
128	3+	0	2+
256	3+	0	4+
512	4+	0	3+

[1] Second day test.
[2] Reactions were measured using the longest dimension of the wheal as follows: ±, questionable wheal; 1+, wheal up to 6 mm; 2+, wheal from 7 to 12 mm; 3+, wheal from 13 to 20 mm; 4+, wheals over 20 mm.
[3] Fourth day test.
[4] Positive control tests.

As expected, CB-1C was more stable in acid than in alkaline solutions. Thus, at 130°, a pH of 8 or higher was required to destroy the precipitating property in less than one hour. Similarly, at 115°, a pH of 9 or higher, or at 130° a pH of 7 or higher was required to reduce the reagin neutralizing capacity of CB-1C to less than 0.026 per cent in less than one hour, respectively. In pH values of higher acidity than those, CB-1C retained demonstrable antigenic and allergenic properties in over one hour's heating at temperatures as high as 130°. Retention of these properties after such drastic heating is unique among antigens and allergens as far as published results are concerned. However, other allergens of the natural proteose classification may be equally stable, because they all retain their antigenic and allergenic properties after being heated for one hour at 100° C in water, treatment used in their isolation.[13]

SUMMARY

The effect of length of time of heating the castor bean allergen, CB-1C, at 100°, 115° and 130° C in sealed tubes at pH values of 4, 5, 6, 7, 8, 9, and 10 on the destruction of precipitating capacity with rabbit castor bean allergen antiserum and reduction of *in vivo* reagin neutralizing capacity to less than 0.026 per cent of the original value with serum of a castor bean sensitive person, has been determined.

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THE IN VITRO SENSITIVITY OF LEUKOCYTES FROM ALLERGIC AND NON-ALLERGIC SUBJECTS TO THE PRODUCTS OF GROWTH OF MICROORGANISMS

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IT HAS BEEN established that the leukocytes of tuberculous animals[1-5] and of human beings[6-9] are specifically sensitive to tuberculin and that the sensitivity of experimentally infected animals can be detected just as reliably by testing for leukocytic sensitivity as by skin testing.[10] It has also been shown[8,11] that there is an apparent relationship between an active disease state in tuberculous subjects and leukocytic sensitivity. Furthermore, Moen[12] has shown that the leukocytes of guinea pigs with streptococcal lymphadenitis are sensitive to extracts of type C streptococci, and Nantz and Blatt[13] have reported that the leukocytes of ten per cent of a group of fifty patients were "injured" by filtrates of cultures of streptococci, staphylococci, and pneumococci when cultured in a fibrinogen-thrombin clot.

It occurred to us that, if a similar relationship exists between active sensitization in allergic individuals and leukocytic sensitivity to bacteria or their products, we might be able to demonstrate it by the *in vitro* technique successfully employed with tuberculous subjects. This study was undertaken to determine whether there is any difference in the *in vitro* sensitivity of the leukocytes of normal subjects and of those from clinically allergic patients to filtrates of broth cultures of microorganisms.

MATERIALS AND METHODS

Cultures.—The cultures of the fourteen species of organisms that were selected for this study were in most cases isolated from clinical material. The five species of pathogenic cocci (*Streptococcus pyogenes, Streptococcus salivarius, Staphylococcus aureus, Staphylococcus albus,* and *Diplococcus pneumoniae*) were selected because they are frequently found in the upper respiratory tract. Three species (*Escherichia coli, Neisseriae catarrhalis,* and *Neisseriae flavescens*) were selected because of their almost constant presence in or on the human body. Two species were selected for their possible relationship to other species (*Aerobacter aerogenes* to *E. coli; Klebsiella pneumoniae* to the coliforms, on the one hand, and to the pneumococcus, in its capsular structure, on the other). The remaining four species (*Proteus mirabilis, Pseudomonas aeruginosa, Streptococcus*

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faecalis, Candida albicans) were selected because of their frequent association with pathological conditions either as contributory or as primary pathogens.

Filtrates.—The filtrates were prepared as follows: Fifty milliliter volumes of brain-heart infusion broth (Difco) or trypticase soy broth (BBL) were inoculated with the organisms and incubated for twenty-four to forty-eight hours at 37° C. The cultures were centrifuged and the supernatant fluids passed through Seitz filters. The filtrates were checked for sterility, placed in screw cap vials, and stored at 4° C.

The migration technique.—This technique was carried out as previously described[8,9] except that various dilutions, ranging from 1:10 to 1:200, of the culture filtrates and of the broth controls were used. The dilution of each filtrate to be used was determined by titration using the leukocytes of apparently healthy subjects.

Subjects.—The subjects used in this study fit into two groups:

Group I.* Apparently healthy non-allergic (no history of allergy, no recent upper respiratory infections)

Group II. Clinically allergic (diagnoses included one or more of the following: asthma, allergic rhinitis, allergic bronchitis, allergic conjunctivitis, allergic dermatitis, and rhinosinusitis), as determined by history, symptoms, examination of nasal smears, skin tests, et cetera.

TABLE I. STATISTICAL ANALYSIS OF CYTOTOXIC INDICES USING LEUKOCYTES FROM HEALTHY SUBJECTS, WITH BRAIN HEART INFUSION AND TRYPTICASE SOY BROTH

Medium	Number of Subjects	Number of Tests	Cytotoxic Index Range	Mean CI $(\overline{X})$	Standard Deviation (S)	2S
Brain heart infusion	6	240	0.92—1.10	1.0002	0.0351	0.07
Soy broth	4	703	0.89—1.14	0.9998	0.0355	0.07

RESULTS

Previous experience with the migration technique[7-10] had led us to expect a range of cytotoxic indices. In order to determine how great a range of indices would be obtained in the absence of a specific sensitivity and to find out the degree of variation within the test itself, a series of tests on the leukocytes of apparently healthy subjects was made, with the brain-heart infusion broth and the trypticase soy broth. Two hundred and forty tests were made with the leukocytes of six subjects using the

*Student volunteers from the University of Kentucky.

brain-heart infusion broth, and 703 tests were made with the leukocytes of four subjects using trypticase soy broth. An analysis of the results is given in Table I.

It can be seen that the cytotoxic indices ranged from 0.92 to 1.10 with a mean ($\overline{X}$) cytotoxic index (C.I.) of 1.0002 and a standard deviation

TABLE II. LEUKOCYTIC SENSITIVITY OF APPARENTLY HEALTHY NON-ALLERGIC AND CLINICALLY ALLERGIC SUBJECTS TO CULTURE FILTRATES OF 14 SPECIES OF MICROORGANISMS

Culture Filtrates	Normal			Clinically Allergic			Ratio* CA/AH
	Number Tested	Positive No.	Positive Per Cent	Number Tested	Positive No.	Positive Per Cent	
A. aerogenes	27	17	62.9	13	11	84.6	1.4
E. coli	34	18	52.9	26	19	73.1	1.4
P. mirabilis	27	13	48.2	13	8	61.5	1.3
K. pneumoniae	33	12	36.4	28	16	57.1	1.6
P. aeruginosa	27	8	28.6	13	7	53.8	1.9
S. albus	55	8	14.5	50	28	56.0	3.9
S. aureus	71	9	12.7	93	45	48.4	3.8
S. pyogenes	27	3	11.1	13	3	23.0	2.0
S. saliparius	71	7	9.9	93	36	38.7	3.9
D. pneumoniae	71	6	8.5	93	19	20.5	2.4
N. flavescens	71	4	5.6	93	8	8.6	1.5
N. catarrhalis	27	3	11.1	13	7	53.8	4.7
C. albicans	27	2	7.4	13	8	61.5	8.3
	33	2	6.1	30	7	23.3	3.8

*Ratio of percentage of clinically allergic subjects to percentage of healthy non-allergic subjects.

(S) of 0.0351 for the brain-heart infusion broth. For the trypticase soy broth the cytotoxic indices ranged from 0.89 to 1.14 with a mean of 0.9998 and a standard deviation of 0.0355. From these findings it was calculated that indices obtained in the future with the culture filtrates that were below 0.93 ($\overline{X}$—2S) or above 1.07 would be due to the effect of substances in the filtrates and not to the variations inherent in the testing method. Those indices that were below 0.93 were considered to indicate an inhibitory effect.

The study was carried out in two parts. In the first part leukocytes were tested using the filtrates from the five species of cocci *(S. albus, S. aureus, S. pyogenes, S. salivarius,* and *D. pneumoniae).* After completion of the first part of the study in which the leukocytes from forty-five normal and eighty clinically allergic subjects were tested, an examination of the data revealed what was considered a definite trend toward a greater sensitivity of the leukocytes of the clinically allergic subjects. It was then decided to extend the study to include more subjects, and the filtrates of nine additional species of microörganisms. The second part of the study was terminated before we could test as large a number of subjects as planned. However, because the results obtained with this last group of twenty-seven normal and thirteen clinically allergic subjects indicate definite trends, the data for all of the tests are included in this report.

Cytotoxic indices obtained with the culture filtrates below 0.93 were

considered positive for leukocytic sensitivity. The number and percentage of subjects in each of the two groups with such indices is given in Table II.

It can be seen from the data here presented that all the filtrates were able to inhibit the migration of the leukocytes of some of the subjects of both groups. The lowest incidence of migration inhibition that occurred in the normal group was obtained with the filtrate of *D. pneumoniae* (5.6 per cent). The lowest incidence that occurred in the clinically allergic group (8.6 per cent) was also obtained with this filtrate. The highest incidence that occurred in the normal group was obtained with the filtrate of *A. aerogenes* (62.9 per cent) and the highest incidence that was obtained in the clinically allergic group (84.6 per cent) was also obtained with this filtrate. It is obvious that although many in the normal group exhibited a high degree of leukocytic sensitivity to some of the filtrates (the first five in Table II), in every case the percentage of clinically allergic subjects exhibiting such sensitivity was higher. With some of the filtrates these differences, as shown by the CA/AH ratios in the last column, were probably not significant (*P. mirabilis*, 1.3; *E. coli*, 1.4; *A. aerogenes*, 1.4; *D. pneumoniae*, 1.5; and *K. pneumoniae*, 1.6). However, with the other filtrates the differences were more marked, ranging from 1.9 with *P. aeruginosa* to 8.3 with *Neisseriae catarrhalis*.

The filtrates that yielded the two largest CA/AH ratios, *N. flavescens* (4.7) and *N. catarrhalis* (8.3), are of special interest. Only rarely are either of these organisms associated with any disease condition but both are almost constantly present on the mucous membranes. However, despite the limited number of subjects tested (twenty-seven normal and thirteen clinically allergic) there was a very marked difference in the leukocytic response to the filtrates of these two organisms. The leukocytes of nearly five times as many clinically allergic patients gave positive tests to the *N. flavescens* filtrate and over eight times as many to the *N. catarrhalis* filtrate as did those of the normal subjects.

The data on the *C. albicans* filtrate are separated from those of the other filtrates because, in some respects, the results with this filtrate may not be a true indication of the effects of the normal growth products of this organism. In order to avoid using an additional broth control the *C. albicans* culture was grown in trypticase soy broth. Although growth was quite good, this medium is not optimal for this organism. Nevertheless, the results show that here again the leukocytes of about four times as many of the clinically allergic subjects were hypersensitive as were those of the normal subjects.

Another indication of differences in the sensitivities of the leukocytes of the two groups of subjects was the frequency of the occurrence of sensitivity to more than one filtrate at the same time. The occurrence of such multiple sensitivities in the two groups is shown in Tables III and IV.

Table III shows the number and percentage of subjects whose leukocytes were sensitive to the filtrates of the five species of cocci used in both studies. It can be seen from this table that the leukocytes of three times as many normal subjects failed to react to any of the filtrates as

TABLE III. MULTIPLE SENSITIVITY TO FILTRATES OF FIVE SPECIES OF PYOGENIC COCCI

Sensitive to	Normal		Clinically Allergic	
	No. Tested 71		No. Tested 93	
	No.	Per Cent	No.	Per Cent
No filtrate	43	60.6	19	20.4
One or more filtrates	28	39.4	74	79.6
One filtrate only	22	31.0	32	34.4
Two filtrates	4	5.6	25	26.9
Three filtrates	2	2.8 (8.4%)	14	15.1 (45.2%)
Four filtrates	0	0	3	3.2

compared to the leukocytes of the allergic subjects (60.6 per cent *vs.* 20.4 per cent). Of the 39.4 per cent of the normal subjects whose leukocytes gave positive reactions, the leukocytes of only 8.4 per cent reacted to more than one filtrate, as compared to 45.2 per cent of the

TABLE IV. MULTIPLE SENSITIVITY TO FILTRATES OF FOURTEEN SPECIES OF MICROORGANISMS

Sensitive to	Normal (27)		Clinically Allergic (13)	
	No.	Per Cent	No.	Per Cent
0	3	11.1	0	0
1	4	14.8 (37%)	0	0
2	3	11.1	0	0
3	6	22.2	3	23
4	4	14.8	1	7.7
5	4	14.8	1	7.7
6	2	7.4	1	7.7
7	0	0	1	7.7
8	1	3.7	2	15.4
9	0	0	1	7.7
10	0	0	1	7.7
11	0	0	2	15.4

79.6 per cent of the allergic subjects whose leukocytes reacted to more than one filtrate, a ratio of nearly 5.5 to 1 in favor of the allergic subjects. Only 2.8 per cent of the healthy subjects had leukocytes that reacted to as many as three filtrates and none had leukocytes that reacted to four. On the other hand, the leukocytes of 15.1 per cent (5.5 times as many) of the allergic subjects reacted to three filtrates and those of 3.2 per cent reacted to four. No one was sensitive to all five filtrates.

The results of the tests with the filtrates of all of the fourteen species

of bacteria on the leukocytes of a limited number of subjects (twenty-seven healthy and thirteen allergic) are shown in Table IV. It can be seen that the leukocytes of only three (11 per cent) of the normal subjects did not react to any of the filtrates. The leukocytes of all of the clinically allergic subjects reacted without fail. As a matter of fact, no leukocytes of any subject in this group reacted to less than three of the filtrates while the leukocytes of ten (37 per cent) of the normal group reacted to less than three. The leukocytes of two of the clinically allergic subjects reacted to eleven of the fourteen filtrates. In this group, the leukocytes of 77 per cent of the subjects reacted to four or more filtrates, as compared to 41 per cent of the leukocytes of the non-allergic, a ratio of about two to one. Again, the total number of positive leukocytic sensitivity reactions in the twenty-seven normal subjects was eighty-four, approximately three per subject, while in the thirteen clinically allergic subjects the corresponding number was eighty-eight, approximately seven per subject. These figures correspond closely to those obtained with the five filtrates used in the first part of the study. In both cases the clinically allergic subjects gave twice as many positive reactions as did the normal subjects.

DISCUSSION

Our results show that the incidence of leukocytic sensitivity in clinically allergic subjects with diagnoses of asthma, allergic bronchitis, allergic conjunctivitis, allergic dermatitis, and/or rhinosinusitis is greater than that in apparently normal subjects. The degree of greater incidence varied with different organisms from 1.3 to 8.3 times. The allergic subjects also showed a much higher incidence of multiple sensitivity. Of the twenty-eight normal subjects who were sensitive to one or more of the five filtrates used in the entire study only six, or 21 per cent, were sensitive to more than one, and of these only four were sensitive to two, and only two were sensitive to three of the filtrates. On the other hand, of the seventy-four clinically allergic subjects who were sensitive to these filtrates, forty-two, or 56 per cent, were sensitive to more than one, and, of these, three were sensitive to four of the filtrates. Similarly with the limited number of subjects whose leukocytes were tested with all fourteen filtrates, ten, or 37 per cent, of the normal subjects were sensitive to two or less, while none of the clinically allergic were sensitive to less than three.

Although these findings indicate that there is an appreciable difference in the sensitivity of the leukocytes of the clinically allergic subjects as compared to those of the normal subjects, the fact that the leukocytes of an appreciable percentage of the healthy non-allergic group gave sensitive responses to so many of the filtrates raises the question of specificity. Is this difference due to a greater and more widespread specific sensitization among the clinically allergic group or to non-specific factors such as greater leukocytic fragility or to a lowered vitality of the leukocytes? Our

data appear to point to a greater specific sensitization. They show that the difference in the percentage of subjects in the two groups that showed sensitivity varied with the different filtrates. It also appears that the clinically allergic subject becomes sensitized more easily to such ubiquitous organisms as *N. flavescens, N. catarrhalis, S. salivarius,* and *C. albicans* than the normal one. Furthermore, it appears that the clinically allergic subject who is sensitive to microörganisms is apt to be sensitive to a greater variety of microörganisms than the apparently healthy subject.

Considering the microörganisms used in this study, it is not surprising that a rather high percentage of the subjects in both groups was found to be sensitive. In fact it is probable that every subject tested had at some time been sensitized to the products of growth of every one of the species used. If this is true, either the clinically allergic subjects retained their sensitivity to a higher degree or their cells are more subject to resensitization than those of the normal subjects. It may also be that the difference in the two groups is due to differences in the degree of sensitivity of the leukocytes. Such a difference might be detected by titration using a series of dilutions of the filtrates.

SUMMARY

By means of a leukocyte migration technique the leukocytes of apparently normal and clinically allergic subjects were tested for sensitivity to filtrates of broth cultures of fourteen species of microörganisms. The incidence of sensitivity was from 1.3 to 8.3 times greater among the clinically allergic subjects than among the normal, depending on the species of microörganism. The leukocytes of the clinically allergic subjects also showed a much greater tendency toward multiple sensitivity than those of the normal subjects. With the filtrates of five of the species (pyogenic cocci) with which the leukocytes of all the subjects were tested, the leukocytes of more than eight times as many of the clinically allergic subjects showed multiple sensitivities as those of the normal subjects.

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THE ALLERGY FOUNDATION OF AMERICA

Plans for the annual meeting of the Allergy Foundation of America are being developed around the theme: "New Frontiers in Allergy." The day-long program will be held at the Waldorf-Astoria Hotel in New York City on May 23, 1960.

Speakers for the day will include Horace S. Baldwin, M.D., Chairman of the Allergy Foundation of America; Justin M. Andrews, Sc.D., Director of the National Institute of Allergy and Infectious Diseases, Washington, D. C.; Bram Rose, M.D., President, American Academy of Allergy; Giles A. Koelsche, M.D., President, American College of Allergists.

Following a luncheon and the closed meeting of the Board of Trustees, there will be a series of private parties and dinners sponsored by the Hospitality Committee of the Foundation. Visiting allergists, their wives and guests will be entertained in the homes of the New York Board members preceding a theatre benefit performance of the Broadway musical comedy hit *Greenwillow* at the Alvin Theatre. This expanded annual meeting, including the open sessions for visiting allergists, is a part of the Allergy Foundation's program of re-organization and development. Every effort is being made to focus attention on American allergists and on their contribution to national health.

The foundation enjoys over-all direction by an eminent group of medical and lay trustees and the counsel and co-operation of allergists throughout the country. The May 23, 1960 annual meeting, the seventh annual meeting, has been planned to recognize and to acknowledge publicly the help allergists have given to the Allergy Foundation.

Allergists have from the outset supported the program and have contributed generously to its work. The annual meeting will be an opportunity to express appreciation of this support. Arrangements for attending the sessions of the annual meeting and for accommodations in New York City can be made by writing to the Allergy Foundation, 801 Second Avenue, New York 17, New York.

SEMANTICS—AND THE FUTURE OF ALLERGY

MAX SAMTER, M.D.
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A PRESIDENTIAL address, by precedent, is an inventory of accomplishments, failures, roadblocks, and advances. In Chicago, Dr. Merle W. Moore reviewed the state of education; I propose to review, today, the semantics of allergy which have haunted us for more than fifty years.

Allergy, certainly, means so many things to so many people. In his last contribution to the history of allergy, the introductory chapter of the third edition of Hansen's text, Rössle examines critically the Greek roots of the word.[1] Von Pirquet had meant to emphasize differences: ἄλλος—the individual's deviation from a pre-existing state, or from the norm, in his *capacity* to react. Yet, ξργον means action itself; and the Greek word which von Pirquet adopted for the creation of the term allergy, ξργεια, does not exist. Taken literally, allergy does not suggest the potential, but the reaction itself—a meaning not meant by von Pirquet, not accepted by us.

The ancestry of some of our other terms is equally dubious: if Richet really wanted to emphasize the loss of protection (φηλαχή), then, Rössle states, *a*phylaxis, not *ana*phylaxis, would have been appropriate and correct.* Idiosyncrasy, on the other hand, is probably the oldest of our classical terms, and refers to a peculiar mixture of the "humors" which distinguishes the individual. The word is mentioned by Ptolemy, but Sextus Empiricus was the first to classify man by body, soul and idiosyncrasies. The word, at that time, had a wider range. Good vision at night, chilliness under the sun, perspiring in the shadow, tolerance as well as intolerance to poison, the ability to eat beef when fish caused indigestion, the heart upset by pepper, diarrhea induced by Lesbian wine, were covered by the term which we have now endowed with a much more specific meaning. Atopy, on the other hand, is a relatively young addition to allergic terminology. As the specialty grew, the need for more precise definitions grew in proportion. In 1923, Coca and Cooke published their paper which divided hypersensitiveness into normal forms which, like serum sickness and dermatitis venenata, represent quantitative variations

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Presented at the Fifteenth Annual Congress of The American College of Allergists, San Francisco, California, March 19, 1959.

*Several weeks after the presentation of this address it was brought to my attention that Kenneth L. Burdon in a discussion—distinguished by clarity and precision—had traced the fate of the term "anaphylaxis." Richet had defined "anaphylaxis" as "the contrary of protection." Stedman's Medical Dictionary introduces the meaning "without protection"; and pioneer American workers in the field initiated the interpretation "against protection," which is "the one now most commonly given in authoritative American textbooks and reviews."[2]

within the species; and abnormal forms which, like anaphylaxis, atopy, and the sensitiveness of infection, are based on qualitative rather than quantitative differences.[3] It seems likely that this scheme, which has served us so well, might have to be abandoned in the light of what we have learned in recent years. It is equally certain, however, that the term 'atopy' will remain—Coca's "strange disease" christened by Dr. Perry of Columbia University. It is an Anglo-Saxon disease, just as para-allergies, hetero-allergies and Heubner's allobioses are strictly European terms for allergic phenomena.

We share the predicament (that our terminology lags behind our understanding) with other disciplines. In a recent review on serotonin, Page offers his apologies:[4]

> "The vexing question of nomenclature continues to plague the scientific world because no adequate rules have been laid down by a competent body of scientists. This failure has led to much needless misunderstanding and often ill feeling. Our own position in the case of serotonin is the usual helpless one; we started the row with the best of intentions but have no idea how to resolve it. 'Enteramine' was given as a name by Erspamer to an active principle contained in tissue extracts, chiefly from the gastrointestinal tract. It had not been isolated or its structure determined. Rapport, Green and I[3] isolated 5-hydroxytryptamine from serum and believed we should give the substance a trivial name that we hoped would be useful and euphonious. With Dr. Corcoran's help, serotonin was coined. Subsequently, a variety of initials such as 5-HT, HT, 5HTA, etc., have been used by others. Enunciation of 5-hydroxytryptamine, especially when repeated several times, has somewhat the effect of popping frying oil on the listener. It is for such reasons we continue to use what seems to us the quite innocuous and euphonious word, serotonin."

Dr. Page's last sentence raises the question which I am about to discuss: whether there really are innocuous words in the world at large, in medicine in general, and, specifically, in allergy.

Semantics, the science of meaning, has existed in one form or another for more than a century. "General Semantics," on the other hand, which is founded on Count Korzybski's "Science and Sanity," is of relatively recent origin, and dedicated to the improvement of thought and communication by analysis and correction of the ambiguity of words and sentences. It is interesting that Ogden and Richards' text on "The Meaning of Meaning"[5] ends with a supplement by Crookshank which examines the relationship between words and what they communicate in medical diagnosis.[6] Crookshank presents striking examples of the haphazard use of references and symbols. It is obvious that science, which must rely on precise and reproducible statements, suffers when the relation between word and meaning becomes obscure. It is this relationship, then, which demands our attention and, perhaps, our initiative, if, as semanticists believe, the words which we adopt are bound to influence our thoughts and, eventually, our actions.

In a readable and informative monograph on "Words and their Use" Stephen Ullmann,[7] of the University of Glasgow, defines "meaning" as a reciprocal relationship between a name and a sense which enables one to call up the other—I see a color and label it brown: saying "brown" will then evoke the image of the color. Yet, words may not only have simple, but multiple meanings, and saying "brown" may very well evoke the image of the Editor of the ANNALS OF ALLERGY. The ambiguity might, at times, be fun and is, of course, the basic fabric of jokes—it is dangerous, indeed, if it creeps into the language of our scientific conclusions.

Definition opens another dimension; it connects an unknown meaning with a meaning which is familiar. To paraphrase an example offered by Ogden and Richards: I have arrived at the air-terminal, downtown: how do I get to the Mark Hopkins Hotel? The air-terminal becomes the point of departure. "Turn right," said the policeman, "and follow the street until you get to the top of the hill." Conceivably, there are several routes—as many as twenty-five have been designed by various semanticists. Each, however, requires a fixed landmark to start with and a description which eliminates faulty alternatives. With assurance, we state that antibodies are γ-globulins—yet, how treacherous is the connection. Do we mean to imply that β-globulins are a different breed of cats which do *not* owe their existence to antigen? Do we suggest that γ-globulins are always, and invariably, antibodies? Or are we guilty of Ullmann's indictment that "terminologies have often been allowed to grow up uncontrolled with the result that all varieties of multiple meaning have freely developed within them;" that, in fact, scientific nomenclature presents a disturbing multitude of examples of "how the same term can denote different things, and the same thing be denoted by different terms."

Allergists have been uneasy, indeed, about their choice of terms. Coca and Cooke were almost apologetic about "atopy" which, they said, "was used in the sense of a strange disease." "However," their paper continues, "it is not, on that account, necessary to include under the term all strange diseases; the use of the term can be restricted to the hay fever and asthma group." It can, certainly, but who will vouch that it is? It would be foolish, even dangerous to suggest that the venerable term be removed from the dictionary of allergy, yet, to use Bühler's criteria, as a *symptom* of the speaker's mind, a *symbol* of the message conveyed, a *signal* to the hearer, atopy is as useless as the essential of essential hypertension, the idiopathic of idiopathic thrombocytopenic purpura. It was the devil, after all, who, in Goethe's "Faust," informed the student that, whatever be amiss in understanding, "a word will surely fill the gap, in time."

The semantics of allergy have completed a cycle. In 1906, von Pirquet defined allergy as altered reactivity: a response to "allergens," foreign substances which induce the allergic state. In 1958, the Committee on Nomenclature of the International Association of Allergology, in a report

which reflects concern and effort, redefined immunity as a quantitative change, allergy as an "acquired qualitatively altered capacity of living tissue to react, induced by a specific allergen." Since allergy must have grown up in more than fifty years—while the Committee's definition is obviously the same as von Pirquet's—it is certain that the word itself has been endowed with attributes which widen the hard core of its original meaning. Words, of course, can be enriched in and robbed of their width and power for many reasons. The wear and tear of careless use, for instance, has made the term idiosyncrasy almost unacceptable. Emotions can outweigh the rational basis of a word: if someone advertises a chemical as a—fraudulent—cure for allergy, its formula might not evoke its structural image, but, as it were, laughter, anger, contempt. The progress of medicine has given a dynamic context to many old and static words: enzyme, now a key-word in our concepts of life, used to be a modest instrument for the digestion of food; adrenal cortex an anatomical oddity of uncertain significance.

Our system of education tends to treat words as instruments of communication and assigns, more often than not, to our mind the role of a passive and objective recorder. Yet, there is ample evidence that the mind, at will, can accept or reject, that the image which the speaker intends to convey is *not* the image which the listener's conditioned brain perceives and stores: allergy, an almost unlimited opportunity for investigation, might well, and simply, be seen as an attractive way to earn a living. Words are measured by past experience; the warped and clouded screen will distort the image which is projected on it. Even abstract terms, unless restrained by philosophers, will differ in impact. Freedom has unlimited meanings, and love is—as semanticists will readily admit since general semantics is an eminently practical science—what love has meant to us.

Words are signs. Signs are "part of an experience which is capable of calling up the remainder of that experience." Ullmann quotes the story of the strip-teaser who was annoyed by the unpleasant connotations of the term. A mysterious Greek word was created, "ecdysiast," which restored her dignity and apparently her success. During this morning's session I admired Ethan Allan Brown's and Mary H. Loveless' semantic skill. Heaven knows whether the "one-shot" approach to seasonal allergies is safe, but the term "repository" has such a relaxed and reassuring sound, while its counterpart, the "multi-visit" treatment, suggests pressure, discomfort, expense. I kept wondering whether the friendly reception would have been the same had "multi-visits" been replaced by "step-by-step, standard immunization;" "repository" by "massive doses suspended in mineral oil" injections.

One of the most dramatic examples of the impact of words on the course of the specialty is Rackemann's division of bronchial asthma into "extrinsic" and "intrinsic" types, and his strongly worded advice that

asthma which begins after middle age "should be considered as due to factors other than allergy until proved otherwise."[8] A fresh wind blew—the reclassification promised a rebirth of interest in the patho-physiology of the disease. Yet, as time went on, the daring concept changed subtly. "Intrinsic" became a catch-all word awarded to *any* asthma not clearly extrinsic, called upon to cover uncertainties, looked at with suspicion. Its future is clearly precarious. It might be with us for a while, yield to what Ullmann calls "the law of diminishing returns" and fade into obsolescence, or it might be rescued by a reincarnation which restores the meaning which it has lost.

If words are endowed with kinetic energy, if terms direct and control the thoughts upon which the future of allergy rests, we can ill afford to be complacent. As one gets older, he becomes more tolerant; but the desire for clarity grows with age. If atopy is predicated on the presence of "reagins," we should be disturbed, indeed, by our awareness that "atopic dermatitis" might well be a "non-reaginic" disease. When I mentioned this morning's panel, I selected the label "immunization" for the therapeutic injection of extracts of seasonal allergens. "Hyposensitization," " desensitization" would have served just as well—the interchangeable terms confess that we do not know whether we immunize, desensitize, hyposensitize. It seems likely that the term which we present to our patients reflects either our notion about the rationale of the procedure, or, at least, our hope that the future will bridge the gap between what we assume to be true and the ultimate truth.

It is this hope, this groping and, at times, desperate determination which we share—forces of considerable magnitude which bring us together because they require our joint initiative, our joint resources.

Ogden and Richards recognize the intangible rewards of such co-operative endeavor in the last paragraph of the Summary of "The Meaning of Meaning." They foresee a better understanding of the influence of language upon thought, and a world from which the phantoms by linguistic misconceptions have been removed: ". . . the way is open," they conclude, "to more fruitful methods of interpretation and to an art of conversation by which the communicants can enjoy something more than the customary stones and scorpions."

No stones, no scorpions in San Francisco: the leisurely journey has brought us to the end of the book. The Mark Hopkins, the destination, becomes the point of departure. I am leaving you with regrets, in gratitude, and with the best wishes of the American Academy of Allergy, for the remainder of the meeting and for the coming year of The American College of Allergists.

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215 North Elmwood Avenue
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BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION

Since February 29, 1960, the Bureau of Medicine of the Food and Drug Administration has occupied temporary quarters at Wake Hall, Twenty-first and C Streets, at Oklahoma Avenue, N.E., Washington, D. C. Mail to the Bureau of Medicine should continue to be addressed:

Bureau of Medicine
Food and Drug Administration
U. S. Department of Health, Education and Welfare
Washington 25, D. C.

INTERNATIONAL SYMPOSIUM ON ALLERGY

The European Academy of Allergy, in collaboration with the Spanish Society of Allergy, has organized an international symposium to be held at Barcelona, Spain, on June 3 and 4, 1960.

Subjects to be discussed are: (1) Evaluation and diagnostic methods used in allergy and (2) Functional exploration of the respiratory and cardiovascular systems in asthma, emphysema and allied disorders.

For further information, letters should be addressed to the Secretary: Mr. Camps, Academia de Ciencias Medicas, Via Layetana 31, Barcelona 3, Spain.

THE MID-SOUTH ALLERGY FORUM

At a recent meeting, the following officers for the current year were elected by the Mid-South Allergy Forum at Memphis, Tennessee:

President.....Dr. Lloyd Crawford
Secretary-Treasurer.....Dr. Oliver S. Matthews

PHILADELPHIA ALLERGY SOCIETY

The following are the newly elected officers for the year 1960 of the Philadelphia Allergy Society:

President.....Charles H. Classen, M.D.
Vice President.....Leonard W. Parkhurst, M.D.
Secretary-Treasurer.....Sonia Stupniker, M.D.

ANTIHISTAMINIC ACTIVITY OF DEXBROMPHENIRAMINE (DISOMER)

Appraisal in Pediatric Allergies

MARIAN OLANSKY, M.D., and SIDNEY OLANSKY, M.D.
Durham, North Carolina

THE ROLE OF histamine in producing allergic reactions remains uncertain even today, but since their introduction in 1942, the histamine antagonists have become accepted medication for prevention and treatment of certain manifestations of sensitivity. Like all clinically useful compounds, they have been subjected to extensive chemical manipulation for the purpose of broadening the margin between therapeutic action and unwanted collateral effects. While a number of satisfactory antihistamines are now available, in most instances, the incidence of side effects at therapeutic dosage levels justifies a continued search for more efficient substances. A recent development, the resolution of a potent racemic compound and the isolation of the active antihistaminic principle from its relatively inert stereoisomer, appears to be a distinctive and chemically sound approach to specificity of action.

In the treatment of respiratory and dermatologic aspects of allergy, halogenated pheniramine compounds have been found exceptionally potent and well tolerated agents. Chlorpheniramine and brompheniramine have achieved wide clinical usage in allergic disease amenable to oral antihistamines. Both of these compounds possess asymmetric carbon atoms, an arrangement giving rise to optical stereoisomerism. Both have recently been separated into dextrorotatory and levorotatory fractions. Pharmacologic studies in laboratory animals have demonstrated that with chlorpheniramine[1] and with brompheniramine,[2] antihistaminic activity resides almost exclusively in the dextrorotatory isomer. Early clinical work with dextro-chlorpheniramine has indicated appreciable advantages in low dosage requirements and few antihistaminic side effects.[3]

Brompheniramine (parabromdylamine), like the chlor-derivative, is a useful and active histamine antagonist in man.[4-7] In doses of 8 to 32 mg daily, it elicits a favorable response in patients with various allergic disorders.[6] Lipman, on the basis of broad clinical experience with at least thirty-five antihistamines, states, "In our opinion, both of these drugs (brompheniramine and chlorpheniramine) have shown a relatively greater

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From the Department of Dermatology, Duke University Medical Center, Durham, North Carolina.
Dr. Marian Olansky is Associate in Pediatrics, Duke University Medical Center. Both Dr. Marian and Dr. Sidney Olansky are presently at Emory University Clinic, Atlanta 22, Georgia.
The dexbrompheniramine employed in this study was supplied as Disomer through the courtesy of Dr. Henry A. Strade, White Laboratories, Inc., Kenilworth, New Jersey.

potency and safety factor on a weight basis, both in animal and human experimental studies, than have the other antihistaminic agents."[7] Untoward reactions to brompheniramine include drowsiness, vertigo, nausea, headache, rash and nervousness with a reported incidence ranging up to 15.5 per cent.

TABLE I. COMPARATIVE ORAL ACTIVITY AND ACUTE TOXICITY IN GUINEA PIGS

Drug	Median Protective Dose (PD_{50}) Mg./Kg.	Median Lethal Dose (LD_{50}) Mg./Kg.	Therapeutic Index LD_{50}/PD_{50}	Relative Safety
Dexbrompheniramine (Disomer)	0.10	190	1900	100
DL-Brompheniramine	0.21	180	900	47
L-Brompheniramine	2.85	173	60	3.1
Diphenhydramine	4.0	280	70	3.7
Tripelennamine	3.2	150	47	2.5

The test drugs were given orally in logarithmically spaced doses to fasted guinea pigs one hour prior to challenge with histamine dihydrochloride (1.1 mg./kg.). A median protective dose was then determined from the number of survivors in each test group. All untreated control animals died in asphyxial collapse within five to six minutes.

As might be anticipated, the dextrorotatory form of brompheniramine is approximately twice as potent as the racemic form on a weight basis. Daily doses of 3 to 6 mg for children and 4 to 8 mg for adults, given to a series of 107 patients with allergic and pruritic dermatoses, accomplished good to excellent objective and subjective improvement in 88 per cent of the cases treated.[8] Dexbrompheniramine exhibited little propensity for causing untoward side reactions during this investigation and only three individuals, representing 2.8 per cent of the group, experienced mild drowsiness while taking medication. On the basis of pharmacologic evidence of the superiority of the dextro-isomer and these preliminary clinical observations, the study reported here was undertaken in a pediatric group. The maleate salt was employed.

CHEMISTRY AND PHARMACOLOGY

Dexbrompheniramine maleate (Disomer) is a d-alpha-(2 pyridyl)-alpha-(p-bromophenyl)-N, N-dimethyl propylamine maleate.

In guinea pigs, determinations of antihistaminic activity following oral administration showed dexbrompheniramine to be approximately twice as potent as the racemic compound and about thirty times more potent than the levo-isomer.[2] Acute oral toxicity studies in the guinea pig indicated that dexbrompheniramine was slightly less toxic than either the racemic mixture or the levo form. These findings are presented in Table I. Compared with the histamine antagonists, diphenhydramine and tripelennamine, dexbrompheniramine exhibited an exceptionally high therapeutic index.[2]

Estimations of the degree and duration of histamine-antagonizing properties of single oral doses of dexbrompheniramine were carried out

in human subjects. A single 2 mg dose of the drug was found to produce an initial histamine-antagonizing response within one hour and a maximum response in about three hours after which there was a gradual subsidence of effect.[8] The pattern of response to an oral dose of 4 mg was similar, although the histamine-antagonizing effect was somewhat more prolonged and attained a maximum approximately one hour later. These results suggested a dosage schedule of 2 mg every three or four hours to maintain a satisfactory level of antihistaminic action.

TABLE II. RESPONSE OF PEDIATRIC ALLERGIES TO DEXBROMPHENIRAMINE

Diagnosis	Number of Patients	Response to Therapy			Dosage Form		
		Excellent	Good	Fair	Tablets	Syrup	Side Effects
Allergic rhinitis	26	5	20	1	14	12	3 drowsy
Contact Dermatitis	13	5	8	0	8	5	1 drowsy
Urticaria (all types)	21	13	8	0	2	19	None
Atopic eczema	10	0	10	0	0	10	None*
Erythema multiforme	4	3	1	0	0	4	None
Miscellaneous	9	3	6	0	4	5	None
Totals	83	29 (34.9%)	53 (63.9%)	1 (1.2%)	28	55	4 (4.8%)

*All of these patients were treated locally with hydrocortisone.

Dosage Schedule

80 cases — 2 mg. q.i.d.
1 case — 4 mg. q.i.d.
1 case — 1 mg. q.i.d.
1 case — 6 mg. Chronotab b.i.d.

METHOD OF STUDY

Allergic states constitute an important treatment problem in children. For this reason and because of the accessibility of a varied pediatric group in a large medical center, dexbrompheniramine was appraised in a series of younger patients. A total of thirty-six females and forty-seven males, ranging in age from two months to fifteen years, were given the drug to suppress acute upper respiratory or cutaneous sensitivity reactions. Allergic rhinitis with edema of the nasal mucus membrane and engorgement of the turbinates, mouth breathing, some rhinorrhea and postnasal drip, and sneezing was the presenting complaint in twenty-six cases. The others required treatment for a typical group of allergic and pruritic dermatoses including contact dermatitis, urticaria of various types, atopy, erythema multiform and skin eruptions of a similar nature.

Dexbrompheniramine was administered either as a syrup containing 2 mg in 5 cc or in tablets of 2 mg. A dosage schedule of 2 mg four times daily was maintained in eighty of the eighty-three patients. One case responded to 1 mg and one required 4 mg four times daily. The remaining patient was well maintained on one 6 mg long-acting tablet given twice daily (Disomer Chronotab®). All patients with atopic eruptions were simultaneously treated with a topical preparation of hydrocortisone. These

patients had been on topical steroids which did not control the symptoms and dexbrompheniramine was then added. The combination gave good results. Medication was continued until symptoms subsided or it was believed that a maximum response had been achieved and no further improvement could be expected. Observations by the attending physician of the promptness and completeness with which distressing symptoms were controlled account to a large degree for the final appraisal of dexbrompheniramine as a histamine antagonist. With older age groups, subjective contributions were also considered.

RESULTS

Response to treatment is summarized in Table II. In all cases, with the exception of one patient with allergic rhinitis, good to excellent results were achieved with comparatively low antihistamine dosage. The one patient showed only a fair response to medication. Satisfactory relief of dermatoses was observed. Pruritus was promptly checked and affected skin areas resolved with treatment. In three cases of urticaria, an excellent response was noted thirty minutes following ingestion of dexbrompheniramine in syrup form. The twenty-six cases of itching, sneezing and rhinorrhea of allergic rhinitis were controlled, and edema of the nasal mucus membrane substantially reduced.

The frequent observation during this study was the exceptionally low incidence of side effects at dosage levels adequate for treatment. Drowsiness, usually of mild degree and in no way interfering with continuation of medication, was the only unwanted effect in this series, occurring in four of the eighty-three cases. Drowsiness, a major complaint with antihistaminic agents, was far less common than reported with equipotent doses of other agents. There were no signs of central nervous system stimulation, irritability, tension, sleeplessness, or tachycardia, and no gastrointestinal disturbances. In general, dexbrompheniramine maleate was well tolerated, and the therapeutic significance of the isolation of histamine antagonizing principle from the potent racemic compound, brompheniramine, appeared to be confirmed by results obtained in this pediatric series.

COMMENTS

Experience with antihistaminic agents over a period of seventeen years has demonstrated that the usefulness of any particular agent is determined as much by side effects encountered as by the amount of symptomatic relief obtained. Sedation is by far the most commonly unwanted effect frequently limiting the daytime use of compounds otherwise satisfactory for prompt control of the allergic reaction. At present, the highest therapeutic index in this class of agents is attributed to the halogenated pheniramines, chlorpheniramine and brompheniramine. The discovery of the racemic nature of these compounds and the subsequent separation of

active antihistamine principle from a relatively inert isomer would appear to be a substantial achievement providing a drug with a desired specificity of action.

The excellence of dexbrompheniramine in the treatment of pediatric allergies is evidenced by low dosage requirements for effective control of symptoms and by the absence of treatment-limiting sedation and other untoward effects. Doses of 2 mg four times daily were adequate for suppression of a typical group of respiratory and dermatologic manifestations of sensitivity in children, and at this level, drowsiness of a mild degree was encountered in only four of eighty-three cases. No other side effects were observed. When compared with the incidence of side effects reported with therapeutic dosage of other antihistaminic agents, these findings are impressive and suggest that the removal of the levoisomer is responsible, at least in part, for excellent toleration.

SUMMARY

Resolution of the potent racemic histamine antagonist, brompheniramine maleate, into component stereoisomers has provided an active antihistamine fraction effective in low dosage and with little propensity for inducing side effects. The finding, in laboratory animals, that therapeutic activity is almost exclusively confined to the dextrorotatory isomer is confirmed by early clinical studies. In a pediatric series, dexbrompheniramine maleate produced a good to excellent response in eighty-two of eighty-three cases of upper respiratory or dermatologic manifestations of allergy. Side effects were limited to a mild degree of drowsiness in four patients. Sedation, a common complaint with antihistamine therapy, was markedly low in incidence and in no way interfered with continuation of medication. Dexbrompheniramine maleate appears to be an especially useful drug, superior in therapeutic index and relative potency to other histamine antagonists including the parent compound.

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EVALUATION OF ISOTHIPENDYL HYDROCHLORIDE (THERUHISTIN) IN SOME COMMON PRURITIC DERMATOSES

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IN 1933, the antihistamine era began when Fourneau and Bovet[1] reported that certain phenolic ethers were capable of inhibiting or counteracting histamine, which was thought at that time to be the common factor in all allergic reaction. It was this property which provided the theoretical basis for their therapeutic application in allergic diseases. The widespread use of antihistamines in dermatology came soon after the encouraging reports of the treatment of urticaria and pruritus with Antergan, the first antihistamine used in man.[2] Urticaria has probably been alleviated by these drugs more than has any other disease, but the antihistamines are not always successful since the necessary high tissue levels are not obtainable.[3]

Another reason for the limitation of efficacy may be that, contrary to early concepts, it is now known that a number of different agents other than histamine are involved in the allergic process. Recent studies indicate that serotonin, heparin, acetylcholine, and other unidentified agents play important roles.[4] Since many allergic dermatoses are not simple histamine reactions, their primary symptom, pruritus, is not completely responsive to antihistamines. However, clinical evidence has shown that they are effective in relieving pruritus produced by causes other than urticarial reaction.[5] This may be explained by the pharmacologic actions other than blocking the histamine. Such actions may be sedative, anticholinergic, local anesthetic effects, decreased capillary permeability and interference with hyaluronidase.[6]

But regardless of the nature of cutaneous response, antihistamines have been a valuable adjunct to dermatology, particularly in the control of pruritus. In two studies of eight commonly used antihistamines, benefit was seen in 58 per cent of 389 patients with allergic dermatoses. Relief of pruritus was obtained in 56 per cent of 389 patients.[7,8]

The antipruritic effect has been of particular interest because it is helpful if pruritus can be relieved while specific therapy is being instituted. In attempting to get satisfactory antipruritic effect, it has been found that increasing the dosage often increases the efficacy.

Antihistamines, however, possess certain limitations. A major disadvantage of antihistamines has been the high incidence of toxicity and side effect, from 20 to 28 per cent.[7,9] Most frequently seen is central nervous system depression, ranging from drowsiness to unconsciousness. In some patients incompletely controlled with antihistamines, the danger

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of toxicity or side effects precludes the use of dosages high enough to be effective.

A new antihistamine, isothipendyl hydrochloride* was of interest because it appeared to be particularly effective in urticaria and contact dermatitis[10,11] and because side effects were minimal.[12,13] In one study, drowsiness was seen in only five of 602 patients[10] and in another series, in only one of 200 patients.[12]

STUDY

On the basis of these reports, it was decided to determine whether raising the dose of isothipendyl hydrochloride would increase the antipruritic effect, but not increase the side effect. First, a pilot study was undertaken to determine the incidence of side effects at a dosage slightly greater than the usually recommended dosage for the compound.

Fifty-eight patients ranging in age from four to sixty years were given 12 to 36 mg daily for two weeks to six months. They had the following diagnoses:

TABLE I.

Atopic dermatitis	12
Infantile eczema	2
Contact dermatitis	15
Chronic eczematoid dermatitis of the hands	9
Pruritus vulvae	3
Urticaria	1
Insect bites	6
Tinea pedis with an id reaction	7
Stasis dermatitis with an id reaction	3
Total	58

Only two patients (3.5 per cent) developed a side effect of drowsiness. Although the antipruritic effect of the agent was not the specific aim of this part of the study, the general impression was that results were equal to those seen with other antihistamines.

It was believed that this pilot study showed the usefulness of isothipendyl hydrochloride and the minimal incidence of side effects. Therefore, it seemed worthwhile to evaluate a higher dosage in the hope of increasing the efficacy of the antipruritic action.

Sixty patients ranging in age from fifteen to eighty-two years were studied during periods of ten days to three months. All patients had dermatoses with the common problem of pruritus. All patients received 24 mg sustained action tablets three times a day (72 mg).

Table II gives the results obtained (graded as excellent, satisfactory and unsatisfactory) as based on the degree of antipruritic effect. Excellent results were obtained in three patients (5 per cent); satisfactory results in forty-eight (80 per cent) and unsatisfactory results in nine (15 per cent).

Drowsiness was seen in three patients (5 per cent) but it was necessary

*Isothipendyl hydrochloride (Theruhistin®) Ayerst Laboratories, New York, New York.

to discontinue the medication in only one. No other side effect or toxicity was found. Complete blood counts, urinalysis and alkaline phosphatase studies were done on ten patients who had been on therapy for two weeks to three months. These studies showed no significant changes.

TABLE II.

	Excellent	Satisfactory	Unsatisfactory	Total
Acute contact dermatitis	2	6	1	9
Contact dermatitis	1	15	1	17
Drug eruption		4		4
Chronic pyoderma with id reaction		1		1
Dermatitis herpetiformis			2	2
Atopic dermatitis		7	1	8
Erythema multiforme		1	1	2
Lichen simplex chronicus		2		2
Chronic urticaria			1	1
Acute urticaria		2		2
Chronic eczematoid dermatitis of the hands		5	2	7
Tinea pedis with an id reaction		2		2
Insect bites (mosquito)		3		3
Total	3	48	9	60

DISCUSSION

The therapy was beneficial in controlling pruritus in 85 per cent of the patients. This response was at least 20 per cent better than would be expected with usual antihistamine therapy. Effectiveness was decidedly increased by the increased dosage, without a concomitant significant increase in the incidence of drowsiness. Such a low incidence (5 per cent) clearly indicates that symptomatic improvement is not due to sedation.

The cases of drug eruption, dermatitis herpetiformis, erythema multiforme, acute and chronic urticaria, insect bites, and some cases of contact dermatitis were treated with antihistamines alone. The other patients were given, in addition, simple conventional local therapy as indicated. The local therapy, of course, was most valuable in the specific treatment, but it was felt that isothipendyl hydrochloride played a definite role in the relief of pruritus.

The marked efficacy and antipruritic effect obtained in contact dermatitis is very interesting. Twenty-four out of twenty-six patients were benefited. Contact dermatitis frequently results from reactions due to humoral factors other than histamine. Therefore, there may be some relationship between the results seen in contact dermatitis and the pharmacologic data[15] indicating that isothipendyl hydrochloride had an antiserotonin action as well as a local anesthetic effect and a pronounced vasoconstrictor activity in the skin.

CONCLUSION

Isothipendyl hydrochloride is of value in the treatment of allergic and pruritic dermatoses because the dosage can be safely increased to achieve maximum effect with minimum side effects.

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OBSERVATION AND EXPERIMENT

Only within very narrow boundaries can man observe the phenomena which surround him; most of them naturally escape his senses, and mere observation is not enough. To extend his knowledge, he has had to increase the power of his organs by means of special appliances; at the same time he has equipped himself with various instruments enabling him to penetrate inside of bodies, to dissociate them and to study their hidden parts. A necessary order may thus be established among the different processes of investigation or research, whether simple or complex; the first apply to those objects easiest to examine, for which our senses suffice; the second bring within our observation, by various means, objects and phenomena which would otherwise remain unknown to us forever, because in their natural state, they are beyond our range. Investigation, now simple, again equipped and perfected, is therefore destined to make us discover and note the more or less hidden phenomena which surround us.—CLAUDE BERNARD, 1813-1878. (From *An Introduction to the Study of Experimental Medicine*, Dover Publications, Inc., New York, 1957, unabridged edition.)

INHALATION OF A BRONCHODILATOR-WETTING AGENT SOLUTION

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BRONCHOSPASM and excessive, thickened mucus in the tracheobronchial tree constitute two of the most pertinent pathophysiological features of asthma. It is not surprising, therefore, that one should attempt to combine in one solution those agents which might be effective in "normalizing" these conditions. Many proprietary cough preparations have been formulated in such an attempt. Indeed, the actual use of combined agents by the inhalation route is not especially new. In this study, the bronchodilator was isoproterenol 1:100 and the mucolytic aerosol solution was one containing sodium 2-ethylhexyl sulfate, 0.125 per cent, and potassium iodide, 0.1 per cent, in sterile aqueous solution.*

Several additional considerations suggest an enhanced effectiveness of such a combination. For example, it would seem likely that the wetting agent would enhance the absorption of the bronchodilator, thereby increasing its effectiveness. If mucus plugs are associated with the bronchospasm, as is often the case, it would seem that relieving the bronchospasm would promote more effective clearing of the mucus plugs. Gay and Long[3] commented on the increase in expectoration using isopropylepinephrine (isoproterenol) alone *via* the inhalation route. Furthermore, since the bronchial network is so diffuse and branching, it would seem that such inhalations would be more effective if an increment of time in the range of several minutes or longer could be utilized in their administration. Therefore, by using a small amount of bronchodilator and a much larger amount of the wetting agent, one would get a wider distribution of the therapeutic mist and more treated areas. In addition, some patients note a drying sensation of the respiratory mucosa with the inhalation of some bronchodilators alone. Some may note slight irritation with a wetting agent aerosol alone. A mixture of the two agents would seemingly offset these mild side effects to some degree.

Isoproterenol has been shown to be a very effective bronchodilator[1,3,4,7] while the mucolytic aerosol solution has been evaluated by Levine.[5] After mixing, the mixed solution deteriorates within twenty-four to forty-eight hours. Therefore the solutions must be freshly mixed before each use according to individual patient's needs and the physician's judgment; however, this is probably a beneficial feature.[2] The medication was used in either a Bennett intermittent positive pressure breathing device with an attached nebulizer, or in a new, small pump-nebulizer-mask† apparatus.[6]

*Kindly supplied as Norisodrine Sulfate, 1:100® and Tergemist® by Abbott Laboratories.

†Supplied by TAMSCO, 7542 South Central Expressway, Dallas.

The solution used in this study was two or three drops of 1:100 isoproterenol solution added to 2 or 3 cc of the mucolytic solution. This volume was administered in approximately ten minutes by the pump-nebulizer-mask device and in approximately five minutes by the positive pressure breathing device.

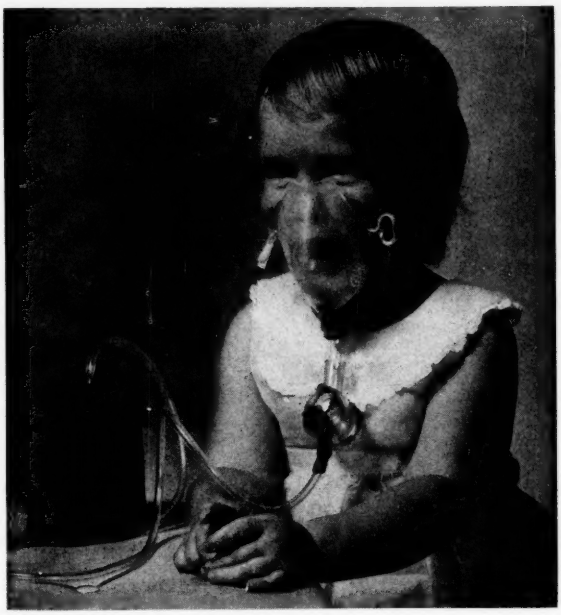

Fig. 1.

The patients were chosen in a consecutive fashion if they had obvious auscultatory wheezing and/or a definite ventilatory defect. Generally, the patients also had to be capable of satisfactorily operating the Collins-Gaensler Timed Vitalometer and of giving reliable evaluation of their pertinent physiological functions. Many of these patients were concomitantly infected, but this feature was not tabulated.

Fifty patients with asthma were treated with inhalations of the isoproterenol and sodium 2-ethylhexyl sulfate mixture. The group ranged in age from five to eighty-seven years, the average age being 27.3 years. Approximately half of the group was given timed vital capacity tests before and after the treatments. Most patients were cautioned against hyperventilating, but an occasional maximal inspiratory effort was encouraged. Approximately half of the group had the mixed solution delivered by the IPPB device, and the other half by the pump-nebulizer-mask apparatus. The end results of the two groups showed no pertinent difference in vital capacity measurements and so were grouped together. The vital capacity tests were done immediately before and after the treatments.

Some patients in the group also had similar treatments as often as four times daily at home, but the results of these treatments were not studied.

RESULTS

Two patients in the group tested showed no change in vital capacity measurements. Generally auscultation showed an obvious improvement immediately following the treatment. No side effects of significance were observed or admitted. Two patients apparently described the bronchodilation as a "peculiar" feeling in the chest. Occasional pulse rate observations before and after the treatment showed no essential change. The group showed an average increase of 21.4 per cent in the 0.5 second vital capacity, and the total vital capacity showed a 20.8 per cent increase. Within several minutes following the treatment, nearly all the patients showed some expectoration and/or clearing of mucus from the nasal passages.

This increase in vital capacity compares favorably with the approximate 15 per cent in the group studied by Segal and Beakey,[8] although much less isoproterenol was used.

CONCLUSION

This study revealed an essential absence of side effects when using, as described, an aerosolized mixture of isoproterenol 1:100, and sodium 2-ethylhexyl sulfate solution for inhalation treatments. Approximately 2 to 3 cc of total mixture was used for each treatment. This mixture requires fresh mixing before each use. Good relief of bronchospasm was achieved by an unusually low dose of isoproterenol. Most patients also showed an easier clearing of mucus from the tracheobronchial tree following a treatment. Such treatments seem to represent an easy and very effective method of producing bronchodilation plus some clearing of tracheobronchial mucus in a group of asthmatic patients seen in office practice. The pump-nebulizer-mask apparatus described represents a convenient, lightweight, and modestly priced addition to the group of available inhalation devices.

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FURTHER OBSERVATIONS ON THE TREATMENT OF HAY FEVER BY HYPODERMIC INOCULATIONS OF POLLEN VACCINE

Historical Document

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PREVIOUS WORK

DUNBAR had described a simple ophthalmo-reaction as a diagnostic test for that susceptibility to pollen which constitutes hay fever; a watery extract of pollen of a certain strength dropped into the eyeball of a normal man produces no effect, but will cause a miniature attack of hay fever in susceptible persons. The test is quantitative in nature, and by noting the dilution of pollen which will just cause the eye to react it is possible to obtain some measure of the patient's susceptibility. Changes in susceptibility presumably have an inverse correlation with changes in immunity to the pollen toxin, and Noon applied this quantitative test to the study of change in immunity produced by subcutaneous inoculations of pollen vaccine. In this way he demonstrated that *suitable* doses of pollen toxin increased the patient's immunity, while unsuitable doses, either did not affect, or even decreased this immunity; this brings the pollen inoculation work into line with the bacterial inoculation work of Wright and his school. These points established, Noon set to work to immunize hay fever patients during the off season in preparation for the season which we have just passed through. Unfortunately, circumstances compelled him to give up work last February, and the research passed into my hands; it is now possible to tabulate some laboratory data about these and subsequent inoculated hay fever cases, and also to give the clinical results of the treatment as disclosed by the past summer season.

LABORATORY AND CLINICAL EVIDENCE IN TABLE

Explanation of table—Adjoined is the tabulated list of the 20 cases treated on this system by hypodermic inoculations of pollen toxin; it is important to note that the list is not a collection of flattering "unsolicited testimonials," but gives an account of every case which had any systematic treatment, excluding only one or two people who were seen once and then lost sight of.

The first column gives the reference number of each case. The cases are arranged in the order in which they arrived for treatment; those who

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From the Laboratory of the Department of Therapeutic Inoculation, St. Mary's Hospital. Published in *The Lancet*, II:814-817, 1911.

This paper is the sequel to Mr. L. Noon's paper on Hay Fever in *The Lancet* of June 10, 1911, in which was described research work for treatment by hypodermic inoculations of pollen toxin. (Dr. Noon's paper appeared in the March 1960 issue, pages 287-291.)

Case	Month and Year	Resistance	Dose	Patient's Opinion	Writer's Opinion
1	July, 1910 May, 1911	40 U.P. 5000 U.P.	4 U.P. 2000 U.P.	Extremely bad with hay fever for last 4 years. Inoculated persistently during the off season; stopped treatment in May. Tested well, but absolutely immune.	Eminently satisfactory
2	July, 1910 (Did not continue)	40 U.P.	2 U.P.	Refused treatment owing to article on anaphylaxis. Had hay fever worse than ever this year.	(Satisfactory)
3	Sept., 1910 May, 1911	20 U.P. 400 U.P.	4 U.P. 120 U.P.	Inoculated irregularly and also with two bacterial vaccines. Had hay fever, but probably not so bad as formerly, and was sooner over.	Disappointing
4	Feb., 1911 May, 1911	20 U.P. 170 U.P.	6 U.P. 25 U.P.	Certainly much better but not clear of hay fever.	Fairly satisfactory
5	March, 1911 June, 1911	40 U.P. 400 U.P.	18 U.P. 20 U.P.	Has been practically free from hay fever this season, but has felt "on the verge of it" once or twice. Went in hay fields, motored, etc. (which was impossible formerly).	Satisfactory
6	March, 1911 June, 1911	70 U.P. 1000 U.P.	12 U.P. 100 U.P.	"Have had no hay fever this year, except one attack lasting an hour after walking through a hay field, and no asthma. In former years had had hay fever for at least six weeks and asthma at night."	Eminently satisfactory
7	April, 1911 July, 1911	6 U.P. 1000 U.P.	2 U.P. 18 U.P.	"I think I may fairly say that though I had it pretty badly occasionally, it was not in so severe a form nor so easily excited. Susceptibility diminished perhaps one-third. Effects less pronounced in the same proportion."	Inconclusive
8	May, 1911 June, 1911	13 U.P. 170 U.P.	4 U.P. 20 U.P.	"Quite a marked improvement, if not an absolute cure."	Moderately satisfactory
9	May, 1911 June, 1911	40 U.P. 500 U.P.	4 U.P. 25 U.P.	This case was handicapped by the inoculation being given rather irregularly. "The attacks were less violent on the whole, and certainly did not last as long."	Moderately satisfactory
10*	May, 1911 June, 1911	130 U.P. 170 U.P.	4 U.P. 10 U.P.	Did not improve after several inoculations, and as he could with difficulty spare the time he decided to postpone the treatment for prophylaxis in the winter.	Failure

11	May, 1911 July, 1911	13 U.P. 170 U.P.	14 U.P. 10 U.P.	Had a little sneezing, but was clear of hay fever most of the time—probably not a very severe case. He reported, "the cure still continues to work marvelously."	Satisfactory
12	May, 1911 June, 1911	40 U.P. ——	4 U.P. 10 U.P.	"I do not want to boast, but I think I am quite done with the accursed thing for this year. There can be no sort of doubt, seeing the kind of season it has been, that I should have suffered, and that severely, if I had not had these inoculations."	Satisfactory
13*	May, 1911 June, 1911	5 U.P. 17 U.P.	1 U.P. 5 U.P.	"I did have a return of the hay fever after the cure" (i.e., three inoculations), "but only slight, and have not had it for over three weeks now."	Satisfactory
14*	May, 1911 July, 1911	170 U.P. 500 U.P.	10 U.P. 15 U.P.	"Since the inoculations began I have had practically no running at the eyes and nose, nor do my eyes get bloodshot."	Fairly satisfactory
15	June, 1911	170 U.P. 500 U.P.	10 U.P. 300 U.P.	A Canadian who gets bad hay fever in August, but not earlier. Has had none this year up to date.	No test
16*	June, 1911 June, 1911	17 U.P. 170 U.P.	1 U.P. 6 U.P.	"She is certain that the condition improved after the third, and she thinks it was better after the second dose. Afterwards she had very little return of symptoms till treatment was discontinued, when there was a slight return."	Satisfactory
17*	June, 1911 July, 1911	5 U.P. 50 U.P.	1 U.P. 6 U.P.	Reported a distinct improvement after the second and third doses, and had no hay fever after the fourth.	Satisfactory
18*	June, 1911 July, 1911	170 U.P. 1700 U.P.	10 U.P. 50 U.P.	Reported himself very much better after the second dose, and was clear of hay fever from June 16th onwards.	Satisfactory
19*	June, 1911 June, 1911	5 U.P. 17 U.P.	1 U.P. 3 U.P.	"The hay fever inoculations, although I came to you having hay fever rather severely, did me an immense amount of good, and I intend next spring . . ."	Fairly satisfactory
20*	June, 1911 July, 1911	17 U.P. 150 U.P.	1 U.P. 5 U.P.	"First inoculation (given during severe attack) gave immunity for 2 days. Second gave complete immunity from Monday till Sunday. Third (rather stronger than before) brought on attack which lasted three days. I have perfect confidence in its power of giving immunity if the right strength is found."	Satisfactory

were already suffering from hay fever when they first presented themselves are marked with an asterisk.

The second column gives the dates of the beginning and end of treatment; these dates refer especially to the parallel figures in the next two columns.

The third column gives the state of pollen-immunity as judged by the ophthalmo-reaction at these dates. The unit of measurement here employed was explained fully by Noon in his paper last June; it is convenient shortly to redescribe it here. The quantitative measurement of the ophthalmo-reaction is made by noting the weakest dilution of pollen extract of which one drop, when dropped on the eyeball, will just produce a slight flushing of the inner canthus of the eye. The unit of measurement is a one-millionfold dilution of Phleum pratense pollen in water—which is spoken of as one unit of pollen, or shortly as 1 U.P. Thus, a hundred-thousandfold dilution of pollen would equal 10 U.P., a thousandfold dilution would equal 1000 U.P. and so on.

The fourth column gives the hypodermic doses of pollen extract which were used at these two dates respectively; these doses are also given in terms of pollen units, 1 U.P. being 1 cubic centimeter of the millionfold extraction, or, to put it another way, the amount of pollen toxin extracted from one-millionth of a gramme of Phleum pratense pollen.

The fifth column gives a short summary of the fate of the patients during the hay fever season this year as reported by the patients or their friends.

In the sixth column, I sum up my own impression of the case.

Laboratory evidence in table.—In studying this tabulated list of inoculated cases, the first point to be noted is the increased tolerance of pollen toxin which was produced by the inoculations in every case. This is shown in Column 3 by the ophthalmo-reaction which the patient gives at the beginning and end of treatment; and as the personal equation, the "functional error," of the observer enters very little into the results of this reaction, it is claimed that this change in the ophthalmo-reaction represents an undoubted change in the immunity of the patient.

Then, again, it is clear from Column 4 that the doses also were increased. Now, it was found by experiment that it was impossible at the commencement of treatment to give much larger inoculations than those indicated in the list without producing symptoms of an overdose—symptoms clinically, and as noted in the laboratory by a falling off in the ophthalmo-reaction. If the dose *were* increased markedly, one might produce even in mid-winter such unpleasant things as swelling, pain, and urticaria at the site of inoculation, a general malaise, and all the nose and eye symptoms of a thorough attack of hay fever. Yet as immunization progressed it was found by repeated ophthalmo-reactions that larger doses could be given with advantage, and though some of these were

enormously greater than the initial dose, they were given without any clinical symptoms and without lowering the ophthalmo-reaction.

Thus, Columns 3 and 4 both denote an increase in pollen immunity during treatment. This increase as here shown varies partly no doubt with the individual, but also with the thoroughness with which the inoculations were undertaken. It might be thought that both an increased ophthalmo-reaction and tolerance of an increased dose were tests of the same thing, and that therefore they must run parallel; this was not the case. At the commencement of treatment the dose could not with advantage be increased as rapidly as the increase of the ophthalmo-reaction, while at the end of treatment there was a tendency to a sticking-point in the ophthalmo-reaction, but the dose could gradually be made larger without producing symptoms either clinical or laboratory.

As denoted by the asterisks, most of the people at the end of the list were already suffering from hay fever when they came, but it was found that in these cases also there was an increase in immunity and an increase in the dose employed. The original scheme was one of prophylactic immunization, and this was much more suitable for the preliminary research work because the effects of each dose could not be obscured by chance doses of pollen from the atmosphere; but clearly phylactic inoculations are of more use if only they will answer reasonably well. At first thought, it might be argued that phylactic doses of pollen toxin will only add poison to an already poisoned patient, but this objection is no more valid in the treatment of hay fever than it is in the treatment of boils by staphylococcus vaccine; the answer is the same in both cases. Though it may or may not be true that at the season of the disease the tissues are over-poisoned, yet the rest of the body may, under the stimulus of an inoculated vaccine, respond by an increased production of antibodies; this surmise is justified when it is found that such an inoculation *is* followed by a demonstrable increase in immunity.

It is claimed that this increase in immunity produced by pollen vaccine is in itself the best proof of the soundness of this line of treatment, whether prophylactic or phylactic. It is true that one does not know if this increase is sufficient for all purposes, but the change is certainly in the right direction, and must be doing good.

Clinical evidence in table.—In judging a system of treatment by "results" there are obvious sources of error which should be taken into account; and in criticizing Column 5 let us give due weight to (1) the natural bias of the operator; (2) the bias of the patient; and (3) outside circumstances—i.e., luck, affecting the results. Every medical man so desires that his patient's condition shall be improved by his treatment that there is a constant tendency to detect such improvement in adventitious fluctuations of health. To avoid this danger most of the results were summarized for me either by the patients or their friends. On the patient's side there is also the desire for improvement, reinforced by the

impression made on the mind by a rather novel system of treatment and a certain atmosphere of "science." As a set-off to such faith-healing, most of the patients had undergone several "cures" which they had been told were infallible, and they therefore submitted themselves to treatment in a critical, skeptical, or even hostile spirit. There is another point: anyone who works at hay fever research will have a highly intelligent and critical material to work with—a very high proportion of the people in the above list have been accustomed by their position or employment to give discriminating judgments. Lastly, luck, or outside circumstances; was this year a better year for hay fever patients? Apparently not. The general, though not universal, opinion seems to be that the season was, on the contrary, more severe than usual—that it began and ended earlier. As some test of the season many of the patients were urged to select another hay fever case as similar as possible to themselves as a control case for observation; all these controls had much worse hay fever than the inoculated patient.

Considering all the cases generally, there seems little doubt that there has been a distinct amelioration of symptoms. This improvement took several forms: a greater freedom from attack, the attack not so bad as in former years, and the attack sooner over, the constitutional disturbance not so great, less asthma. The people who had already developed hay fever when they commenced treatment were, perhaps, the most generous in their comments, possibly because they had recently had a reminder of what hay fever was like.

APPLICATION OF TREATMENT

Diagnosis.—It remains to be considered how this treatment is to be turned to account prophylactically next winter and spring, and phylactically next summer. Whatever the treatment, the diagnosis is important; though an uncomplicated case will usually present no difficulty, yet it is sometimes convenient to have a test of susceptibility to pollen toxin, and this is almost a necessity when prophylactic inoculations are to be commenced in the off season. But there are many reputed cases of hay fever which are partly, and even wholly, caused by a bacterial infection; indeed, it seems probable than an attack of hay fever may be the starting point of a bacterial infection, or that a catarrh of the air passages may predispose to hay fever, and before treatment of any kind it is essential to disentangle these two factors. During the present research several so-called hay fever cases were excluded from treatment because the eye-ball was unaffected by pollen toxin—one of these confessing to malingering, and the remainder being the victims of bacterial infections. A case treated by a colleague is a good illustration of the value of a diagnostic test. A lady reported to have hay fever had slightly inflamed eyes which streamed with clear tears; as she did not react to pollen toxin, hay fever was excluded. The tears were found to be swarming with staphylococci, a vaccine was made, and in a short time the symptoms disappeared.

In the list of cases treated last season, the first ophthalmo-reaction will be seen to vary between 5 U.P. and 170 U.P.; those who did not react to 5000 U.P. were said to give a negative test; there were no unaccountable cases—i.e., people whom subsequent events proved to have been negative giving positive results, and *vice versa*.

Initial dose.—Whether or not the help of such a test is required in fixing the diagnosis, it will at any rate be required in fixing the initial dose should vaccination treatment be decided on. Noon suggested as a suitable initial dose one-third of a cubic centimeter of that dilution of pollen toxin which gives the ophthalmo-reaction. On this plan a man giving a diagnostic reaction of 6 U.P. would receive 2 U.P. hypodermically, and a man who reacted to 100 U.P. would receive 33 U.P. This seems to be about correct, or perhaps to err on the side of over-dosing, especially when hay fever is already developed. In this connection, it should be said that the cases in the tabulated list are not all to be taken as models, as experience was being gathered all the time. In addition, there were several deviations from the ideal course to suit special circumstances.

Subsequent doses.—The patient was, as a rule, re-inoculated every week or ten days; the larger doses were given after a longer interval, while the very small doses were repeated after three to four days. Those cases which were being treated phylactically usually finished treatment with the fifth or sixth dose, the prophylactic inoculations were naturally much more numerous, as an attempt was being made to produce as high an artificial immunity as possible *(sic)*.

All these doses were determined with the assistance of ophthalmo-reactions. These were taken not only at the time of inoculating but also frequently between the doses; and it is urged that whenever this is possible it enables the operator to mark the success of his treatment, to detect mistakes, and, if necessary, to adapt his doses to the idiosyncrasies of his patient. Clearly that dose should be selected which will give the greatest increase to the immunity of the patient; if a dose or a series of doses fails to increase the patient's immunity as measured by the opthalmo-reaction, then it is to be presumed that the dose is either too small to be efficient or so large as to be overdosing the patient, and this latter will be the case if the resistance of the patient is not only not increased but is even diminished after the doses. As a result of such tests it was generally found advisable not to increase the dose quite as rapidly as the increase in the ophthalmo-reaction, at any rate at first. Later in the process of immunization the ophthalmo-reaction ceased to rise so quickly, and it was sometimes possible to regain the 1:3 ratio between the dose and the reaction. Lastly, in the case of very highly immunized patients—e.g., Case No. 1—the ophthalmo-reaction at last became stationary, but the dose was still increased.

It is, perhaps, possible by the ophthalmo-reaction to detect three stages in immunization. In the first stage favourable doses are followed by an immediate rise in resistance, but should not be followed by a corresponding increase in the size of the next inoculation. In the second stage, a larger dose is required, giving first a slight negative phase followed by a slow rise in immunity. In the final stage the eye reaction becomes stationary, but apparently the doses may be increased with advantage so long as there is no evidence, either laboratory or clinical, of an overdose.

Rule-of-thumb inoculations.—Owing to the nature of hay fever there is no danger to life and only temporary danger to health by inoculating "blindly"—i.e., without controlling the doses by ophthalmo-reactions; but it is thought that in order to make a diagnosis and to fix the first dose, at least one eye-testing will be necessary. As a rule-of-thumb, the second and third doses seemed to be usually half as much again as the first dose, while the fourth, fifth, and sixth are perhaps twice as much as the first, though in several cases the size of the dose was increased more rapidly than this.

Pollen supply.—With regard to the pollen extract necessary for testing the eye and for injecting as a vaccine, Dunbar's method of extraction is to be followed. The brief directions given by Noon in the previous paper should enable anyone, who has sufficient time and a laboratory, to construct his own pollen dilution. This will prove inconvenient to many, and it is proposed that the Inoculation Department of St. Mary's Hospital shall make arrangements to put these dilutions of pollen toxin on the market through Messrs. Parke, Davis, and Co., the proceeds to go to the upkeep of the department as in the case of their bacterial vaccines.

A final word as to the species of pollen employed. Noon selected that of timothy grass *(Phleum pratense)* because the pollen of this grass gave in his hands the strongest extract as tested on the eyes of the patients. This spring, I tested various pollens as they matured, rushes, sedges, grasses, etc., but none gave so strong an extract as this timothy grass. The pollen of *Alopecurus pratensis* gave good results, but only possessed one-quarter the strength of *Phleum pratense.* The grasses and flowers dreaded by the hay fever patients differ considerably in different cases, and the question arises—Is one kind of pollen more active in one case and another in another case? Though the question cannot be regarded as settled, apparently this is not so. For one reason, the ratio between the strength of, say, a phleum extract and an alopecurus extract remains about the same with different patients—i.e., 4:1. Furthermore, a patient inoculated with alopecurus pollen vaccine is found to become immune to the phleum pollen extract as tested by the ophthalmo-reaction. Apparently, therefore, we need not select different types of pollen for treating different patients.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

"WITH WHAT WE MUST CONTEND"

The patient who was treated in accordance with the results of the tests listed below was referred because of an angio-edema, which followed the ingestion of two tablets of "Empirin." She also suffered from pollen-caused allergic coryza and seasonal bronchial asthma, and responded with bronchospasm to environmental inhalant allergens. Atopic and contact dermatitis, each affecting the typical sites of predilection, were both present.

The only treatment prescribed was the elimination of the "XXX"-marked substances, (the usual device [*sic*] follows those items listed to emphasize the spelling of the original report). The patient used an ointment consisting of "goat's milk curd," lanolin, and zinc oxide, as applied to both types of dermatological lesions. Nothing else was done despite three years of symptoms affecting all parts of the respiratory tract.

Allergy Tests
Negative — Positive XXX

Direct Contacts

Camel Hair	XXX	Dogwood	XXX
Cat Hair	XXX	Laurel	XXX
Dog Hair	XXX	Goat Hair (*sic*)	—
Feathers, Mixed	XXX	Sheep Wool (*sic*)	XXX
Chicle	—	Lilacs in bloom	XXX
Flaxseed	XXX	Fresh new mown hay	XXX
Dust	XXX	Nylon	XXX
Horse Serum	XXX	Cotton	—
Soaps with detergents (Use Ivory Flakes Liquid and Borax for bleach)	XXX	Quincy (*sic*)	—
		Silk	—
		Tobacco	XXX
Fly Spray	XXX	Rayon	—
Turpentine	XXX	Kerosene	XXX
Poison Ivy	XXX	Floor Wax	XXX
Moth Balls	XXX	Ray Weed (*sic*)	XXX
Needle Grass (*sic*)	XXX	Creasote (*sic*)	XXX
Pollens of Maple and Oak in the Spring	XXX	Golden Rod (*sic*)	XXX
		Sumac	XXX
Dried Leaves in the Fall of the same as above	XXX	Rose Bushes (*sic*)	XXX
		Cutting Wet Grass (*sic*)	XXX

Foods		*Milk Products*		*Meats*	
Apples peeled	—	Cow's Milk	XXX	Lamb	—
Barley	—	Cream	XXX	Beef	—
Bran	—	Ice Cream	XXX	Liver	—

Foods	
Cabbage cooked	XXX
Raw Cabbage	—
Celery	—
Cantalope *(sic)*	—
Watermelon	XXX
Cherries	XXX
Any small seeded fruits	XXX
Cinnamon	XXX
Cocoa and Chocolate	XXX
Coffee 1 cup a day	—
Corn	XXX
Carrots	—
Squash	—
Lettuce	—
Sweet Potatoe *(sic)*	XXX
String Beans	—
Peas	XXX
Tomatoes	XXX
Potatoe and Rice *(sic)*	—
Potato Chips	XXX
Nuts	XXX
Pickles	XXX
Bisquick	XXX
Graham Flour	XXX
Cucumbers	XXX

Milk Products	
Sherbet	XXX
Fish	
Lobster	XXX
Oysters	XXX
Shrimps	XXX
Clams	XXX
All Fresh Water Fish	XXX
Tuna Fish Water Packed	XXX
Codfish	XXX
Desserts	
Jello	—
Gelatin	—
Cake, egg yolk only	—
White of egg	XXX
One-crust pies made with Crisco	—
Chocolate and Cocoa	XXX
Custard	XXX

Foods	
Chicken—no skin	—
Turkey—no skin	—
Duck	XXX
Veal	—
Cheese	
Store Cheese	XXX
Cream Cheese	XXX
Pot Cheese	XXX
Swiss Cheese	—
Blue Cheese	—
Butter	XXX
Margarine	—
Fruits and Juices	
Orange and Juice	XXX
Pineapple	XXX
Cider	XXX
Lemon	—
Peaches, canned	—
Apricots	—
Banana	—
Strawberries	XXX
Prunes and Juice	XXX
Blueberries	XXX

Medications	
Aspirin	XXX
Sulfur and tar products *(sic)*	XXX
Penecillin *(sic)*	XXX
Terramycin	—
Aureomycin	—
Iodine	XXX
Sleeping Pills of Any Kind	XXX
Mercurochrome	—

Can use Bufferin, Anacin, Empirin

CREATIVITY

"True creativity is as rare in science as it is in literature and the arts. It is revealed by the ability to crystallize meaningful concepts out of observations which at first glance are chaotic and patternless. The creative scientist searches for the comprehensibility and the underlying unity in the structure of the universe. He also recognizes that at any time these approaches to concepts of unity are but temporary, partial successes which must inevitably be replaced by new developments and new concepts."—GEORGE SCHWARTZ and PHILIP BISHOP, Preface to *The Origins of Science*, Vol. 1, Basic Books, Inc., New York, 1958.

Progress in Allergy

DERMATOLOGIC ALLERGY VI

Critique and Review of the Recent Literature

(Conclusion)

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MISCELLANEOUS ALLERGIES AND BRIEF REVIEWS

Lobitz and Jillson[108] discuss various aspects of dermato-allergy. The "atopic reagin" is reviewed briefly and the physiologic factors concerned with cholinogenic urticaria are also discussed. In a patient with annular urticaria, skin tests of the immediate wheal site were made to three suspected antigens, wool, molds and feathers, both inside and outside the whealing areas. Wool and molds were positive inside and outside the whealing areas, while feathers did not react inside the lesion but did react outside the involved area. Hence, a specific local tissue anergy was thought to be demonstrated, and the specificity resided only with the feather antigen. Clinically, avoidance of feathers resulted in a cure in this case. In the eczema problem, the histologic finding of spongiosis is explained only by an antigen-antibody mechanism. While experimentally produced allergic eczema in animals and in man is made worse by stress, there is no evidence that spongiosis has ever been produced by stress alone in the absence of an antigen-antibody reaction. The time element in skin test response to sensitization results in a wheal read in a fifteen-minute period; a delayed papule which is read in twenty-four to forty-eight-hour reaction, and an eczematous plaque which may be seen in fungous sensitization studies in one week. It is of interest, however, in patients infested with Trichina, that early in the course of the trichinosis the skin test will be positive as a delayed papule at forty-eight hours and later in the course of the disease the skin test will be positive as a wheal read in fifteen minutes. In superficial fungus infection in man using the Tri-

chophyton antigen, the first skin test reaction will show an eczematous plaque appearing about five days after the test. If the host is exposed to more antigen, the skin reaction will be positive as a delayed papule at forty-eight hours. In patients with long-standing Trichophyton rubrum infections, the skin test reaction will be an immediate wheal. The papers of Strauss, Kligman, Derbes and Caro are recalled, which show the relationship of protein antigens and pre-existing dermatitis. An additional patient is presented who had a long-standing atopic dermatitis; a severe, immediate wheal reaction was produced by injection of mold antigen; this was followed by an attack of severe bronchial asthma in four hours —the patient's first attack. It was suggested that the dermatologist apply these principles as well as those of skin testing to the practice of dermatoallergy.

A sound presentation of the allergic dermatoses is recorded by Rostenberg.[178] Classifications are discussed to help understand allergic or quasi allergic relationships. A primary allergic dermatitis is defined as one in which the cutaneous lesions develop as a direct consequence of the antigen-antibody union. A non-primary allergic dermatitis is one in which there is some relationship to the allergic process without mediation of antigen-antibody reaction. The non-primary classification includes secondary allergic dermatitis in which lesions are exacerbated by an antigen-antibody union; a tertiary allergic dermatitis in which there is a reasonable correlation between skin lesions and an allergic state, and a composite allergic dermatitis which has a conjoint mechanism depending on the presence of infection and development of sensitization to this. With this in mind the allergic dermatoses (primary) comprise: dermatitis venenata, urticaria (some), erythema multiforme, id reactions, erythema nodosum, cutaneous allergic vasculitis and some drug reactions. Non-primary (secondary) dermatoses include drug reactions (some), and atopic dermatitis (few). Tertiary includes atopic dermatitis (most). The composite group is comprised of infectious eczematoid dermatitis and multiform erythemas.

According to Raffel,[166] immunologic mechanisms responsible for diseased states may be divided into two general groups: those producing hypersensitivity and those producing cytotoxicity. In the first group, depending upon an antigen-antibody mechanism, may be listed anaphylactic shock, atopic hypersensitivities, serum sickness, and vascular allergies. Evidence would suggest that rheumatic fever, disseminated lupus erythematosus, rheumatoid arthritis, glomerulonephritis and demyelinating encephalomyelitis could also be placed in this group. Cytotoxicity has a number of mechanisms. Iso-antibody involves two individuals of the same species: transfusion reactions and erythroblastosis fetalis. Individuals who become reactive to their own tissues have an auto-antibody, represented by hemolytic anemias, idiopathic thrombocytopenic purpura and agranulocytosis. Antibodies may be directed against surface-adsorbed substances

on the cell. Examples of this are drug-induced anemia, purpura and leukopenia.

Nelson[136] discusses tissue electrolyte changes in anaphylactic shock in mice. Data obtained early in the course of these investigations indicated a standard pattern of deviation in electrolyte changes and it was thought that these changes could be inhibited by corticosteroid compounds. Anaphylactic shock in the mouse is characterized mainly by an elevation of all tissue electrolyte levels with the exception of potassium in bone. The incidence of fatal anaphylaxis in the corticotropin-treated animals was only slightly less than that in the untreated sensitized mice. Pretreatment with DCA (11-desoxycorticosterone acetate) not only does not prevent fatal anaphylaxis in the challenged animal, but actually increases significantly the incidence of fatal shock. Reserpine and chlorpromazine will protect mice against fatal anaphylaxis almost as well as cortisone if sufficient dosage is given. Compounds with antiserotonin properties can protect mice from the devastating effects of anaphylaxis. One such agent is 1-benzyl-2-methyl-5-methoxy tryptamine (BAS). This is the benzyl analogue of serotonin which appears to act as a specific antagonist of serotonin in living animals.

Immunization against superficial fungous infection in experimental animals is reported by Keeney and Huppert.[91] A strain of Trichophyton mentagrophytes was used. A detailed report of preparation of the antigenic material is described. This destroys the fungus but extracts the antigens in as nearly their native state as possible. A good deal of the procedure is carried out with a cooling apparatus which maintained a temperature of less than 5° C. throughout a continuous operating period of at least fifteen hours. The antigen was then suspended in carbowax 1500 and shaved guinea pigs were given daily applications of this salve for six weeks. A total of eighty-eight guinea pigs was used for their experimental animal work. Of the animals in the control group, 95 per cent developed severe lesions when exposed to infection, whereas only 14 per cent of the treated animals developed lesions of comparable severity. From these data it would seem possible to induce a state of increased resistance to this type of superficial fungous infection by the local application of antigens extracted from the fungus. A relative immunity was present in only slightly less degree one month after the immunization inunction process. Huppert and Keeney[79] continued their immunization studies against superficial fungous infection by using human volunteer subjects. In addition to the Trichophyton mentagrophytes antigen, a culture of Alternaria was likewise studied. The ointment containing the fungous antigen was applied to the right foot of each subject and the control salve to the left foot. At the end of the four week treatment period, infection was introduced by roughening the skin of the fourth web of each foot with a gauze pad. A disk of a two week growth of Trichophyton mentagrophytes was placed in the fourth web of each foot so treated and

strapped with adhesive tape. The inoculum was removed after two days. Active fungous infection developed in seven of nine patients. Five of the nine showed a more clinically active and progressive infection on the control foot (Alternaria) as compared to the treated foot. Further studies were made in thirty-one subjects who passed the screening tests. Results with the thirty who remained throughout the experiment were studied statistically. Analysis of the results indicated that acquired resistance developed in those subjects treated with T. mentagrophytes antigen.

A number of cases of persistent papular lesions of a granulomatous type due to use of stick type deodorants has previously been reported by various authors in these reviews (Progress in Dermatologic Allergy V, 1959). Hurley and Shelley[80] describe their experience with this disorder. Following their clinical experience with experimental studies, the authors believe that these axillary granulomas are the result of zirconium deodorants and operate as specific allergic hypersensitivity reactions to the metal zirconium. This appears to be the first demonstration in man that an allergic process may be responsible for the formation of a granuloma. The granulomas persist for months and treatment is not effective. Most subside spontaneously after about two years. Sneddon[195] comments on the work of Shelley and Hurley[183] on zirconium granuloma. This was produced in the skin of a sensitized subject by the introduction of high dilutions of zirconium under the skin. Sneddon produced a sarcoid-like granuloma after a positive patch test with beryllium sulfate in a case of beryllium disease (1955). This was repeated in a second case and the results were published in 1958.[194] Shelley and others[184] undertook a study to explore the possibility that sarcoidosis may represent an altered, that is, allergic, reaction to simple chemicals. The work of these investigators with zirconium and sarcoid reactions found in under-arm deodorants led them to this present study. It was impossible, however, to uncover any sensitivity reaction to seventy-one different inorganic elements in thirty-five patients with sarcoidosis. The Kveim test remains as a consistent but as yet chemically indeterminate means of often reproducing the disease in patients with sarcoidosis.

Israel[82] and others made a further study of the Kveim reaction in sarcoidosis and tuberculosis. Previous experience had shown that the Kveim reaction was not a reliable aid in the diagnosis of sarcoidosis. In this study, sixty patients with sarcoidosis and forty patients with pulmonary tuberculosis were tested. With the material in this study, 25 per cent of patients with sarcoidosis were found to have a positive Kveim test. In patients with tuberculosis the test gave negative results. Variability of the test material appears to be the important cause for inconstant results of different investigators. The strongest advocates of the Kveim test are usually dermatologists, while physicians and surgeons are accustomed to the use of aspiration biopsy of the liver, intercostal

biopsy of the lung and resection of scalene fat pads and their nodes for diagnosis of sarcoid disease. While the Kveim test is an immunologic phenomenon of interest, it does not seem to be sufficiently reliable from these studies. Nelson[135] believes in the high degree of specificity of the Kveim test in sarcoid disease. The sensitivity of the test depends on the individual patient and the state of his disease or whether he is under corticosteroid therapy. The testing material must meet the requirement of suitable sensitivity of high order; otherwise it should be discarded. The results of the Kveim test should be positive in 70 to 90 per cent of patients with sarcoidosis if suitable antigen is used.

An interesting case of agammaglobulinemia was reported by Slavin[190] and others because is was postulated in 1941 that the patient was suffering from a defective antibody formation and the condition was recognized as agammaglobulinemia in 1942. Since the patient had a normal childhood, it is assumed that he had the acquired rather than the congenital form of agammaglobulinemia. Precipitins developed after hyperimmunization with unrefined horse serum. Skin sensitivity to tuberculin, sulfathiazole and horse serum had developed in this patient. The patient died at the age of twenty-nine. It was noted that there was proliferation of the reticulum of lymph nodes together with complete absence of plasma cells from the lymph nodes and spleen. These were significant findings in view of the role of the plasma cell as a site of antibody production.

Gamma globulin in the serum of normal persons inactivates *in vitro* 20 to 40 per cent histamine. Tappeiner[206] and others report that the examination of "histamine pexis" in 440 patients with various dermatoses showed less than 20 per cent histamine in the majority of dermatoses with allergic etiology, such as chronic urticaria, and drug dermatitis. A normal captant of 20 per cent and more was found particularly in generalized and localized eczema. Psoriasis always showed more than 20 per cent, whereas generalized pruritus and erythema multiforme showed values below 20 per cent. Lack of histamine pexis or values below 20 per cent are supposed to be characteristic of allergic persons.

The syndrome of eczema, thrombocytopenic purpura and recurring infections is a familial disorder which affects only males, and is a sex-linked, mendelian-recessive characteristic. Reports of four cases observed by Mills and Winkelmann[123] are recorded. The skin changes ranged from infantile eczematoid states to exfoliative dermatitis. The case reports concerned infants two months, three months, six months and two and one-half years of age. The most specific cutaneous sign is the presence of a petechial or purpuric eruption anywhere on the skin or mucous membranes. Furuncles and abscesses are common and are resistant to therapy. The prognosis is poor and children usually die within the first four years of life. There are no abnormalities of the protein fraction or deficiency of gamma globulin.

Seventy-seven patients with systemic lupus erythematosus were studied

by McCombs and Patterson[119] with reference to factors influencing the course and prognosis of the disease. The disease occurred much less frequently in men but was more severe and accompanied by a higher mortality than in women. The prognosis was grave when the disease began in patients less than twenty-one years of age; it was more favorable when the diagnosis was established in patients past the age of forty-five. Renal involvement was the most serious abnormality. Patients with polyserositis and myocarditis, when not associated with renal failure, did respond to steroid therapy as did those with encephalitis. Hemolytic anemia and thrombocytopenic purpura in the course of established disease had a grave prognosis. Pregnancy seemed to precipitate some cases of systemic lupus erythematosus. Corticosteroid therapy had a suppressive effect upon the rash, fever, pleurisy, pericarditis, peritonitis, pneumonitis and hematologic and neurologic complications. Many studies have been made concerning the immunologic relationships and finds in disseminated lupus erythematosus (Pasher and Borota[141]). So-called pre-L.E. cells were thought to be decomposition forms of cellular disintegration in the peripheral blood. The latex agglutination test, which has achieved considerable importance in rheumatoid arthritis, was also studied by Christian[38] and others with reference to disseminated lupus erythematosus. Positive latex tests were obtained in nineteen of twenty-four patients with known disseminated lupus erythematosus. Studies of the L.E. phenomenon were also made by Miescher in 1957, and a simple precipitation test for systemic lupus erythematosus was evaluated by Jones and Thompson.[85] Studies with fluorescent antibody have been made by a number of authors in disseminated lupus erythematosus. The reviewer notes that various attempts are being made to evaluate skin tests in patients with proven disseminated lupus erythematosus using various blood fractions from proven cases (Peter Bent Brigham Hospital, Boston, Massachusetts).

Purpura associated with hyperglobulinemia and systemic lupus erythematosus in a woman aged forty-four is described by Reiss and Feiwel.[171] In 1947 epilepsy had developed. When she was seen ten years later, purpura and joint pains had been present for eight months and she was apparently sensitive to phenytoin. Among other studies, serum proteins were recorded as 9.8 gm per 100 ml, albumin 4.5 gm and globulin 5.5 gm. Electrophoresis showed gross increase of gamma globulin, particularly gamma-2. Cryoglobulins were absent. A period free from all drugs did not reduce the purpura. Purpura should be considered a cutaneous vasculitis which is part of her systemic illness. Böttiger[24] reports that a simple precipitation test for systemic lupus erythematosus required critical evaluation before it could be considered acceptable. It is known that there is an increase of the gamma globulin fraction in the serum in systemic lupus erythematosus. Examination of 158 sera with the precipitation test of Jones and Thompson seemed to indicate that the test was not specific for systemic lupus erythematosus but rather dependent on the gamma

globulin content of serum. A patient with hydralazine-induced lupus erythematosus is described by Siguier[187] and others in the French literature. Hydralazine (Apresoline) hydrochloride in a daily dose of 300 to 350 mg was prescribed for a forty-nine-year-old patient because of persistent headache and hypertension. Although he was advised to stop taking the drug, the patient continued to take it for about fifteen months. This was followed by the appearance of violent pains in ankles, knees, wrists and finger joints, and was accompanied by fever, anorexia, chills and general malaise. Soon a typical butterfly eruption appeared and a diagnosis was made of acute disseminated lupus erythematosus following Apresoline therapy. All signs and symptoms disappeared in three months after use of the drug was discontinued.

Dameshek[42] believes that the various hematologic abnormalities seen in disseminated lupus erythematosus, including the L.E. factor, may be considered "auto-immune" in character. He believes there is a development of auto-antibodies against various antigens in the blood cells or plasma. The L.E. factor may be an abnormal auto-antibody directed against some constituent of the leukocyte nucleus. Since disseminated lupus erythematosus occurs principally in women, there is the possibility that an antigen may develop in the menstruating endometria. Alterations occur at monthly intervals in blood cells, blood plasma constituents and small blood vessels. In certain women, these altered factors may become auto-antigenic against both blood constituents and small blood vessels. This may then be followed by the symptom-complex of disseminated lupus erythematosus.

Various clinical types of vasculitis appear in the literature from time to time. The skin lesions in hyperergic vascultitis may vary from erythema multiforme to nodular purpura-like or gangrenous lesions. Matras[115] described the case of a five-year-old boy who developed swollen joints, fever and erythema multiforme-like skin eruptions following extraction of purulent tooth roots. The condition progressed to the point where severe necrotic gangrenous skin changes occurred over the buttocks, upper and lower extremities and sacral areas. These attacks continued and the boy died two and one-half years after the onset of the disease. The reviewer has a similar patient under observation at the time of this writing. The patient is a thirty-year-old woman with disseminated lupus erythematosus. Blood changes are consistent with this disorder. Dry mummification of the fingers of both hands and progressive mummification of the left foot have developed. If she survives, the involved phalanges will drop off. It is surprising that the patient complains very little of the involved areas and shows only minimal febrile reaction, although she is taking full doses of steroids and antibiotics. This, too, may be an example of hyperergic panvasculitis in a patient with diffuse collagen disease. In this connection, Duperrat and Monfort[48] believe that allergy is the underlying basis for Gougerot's nodule allergides, periarteritis nodosa, nodular vascu-

litis, Bazin's erythema induratum, migrating thrombophlebitis, Weber-Christian disease and erythema nodosum. These authors discuss dermal vascular allergies, emphasizing the large group of lesions which appear in sensitized subjects. These include erythema induratum of Bazin, erythema nodosum and certain nodular disorders which appear and disappear rather rapidly without ulcerating. The pathologic elements center about a diseased vessel; necrosis is common, and granulomatous changes are secondary. The allergic nature of the lesions is demonstrated by the nodular allergide of Gougerot and a certain number of nodular vascularitides, which would include periarteritis nodosa, some of the erythema nodosum group and migratory thrombophlebitis. Vilanová and Aguade[214] report six cases of nodular vasculitis in which the lesions are assumed to be etiologically related to aphthosis (Behçet's syndrome). Intracutaneous injections of an antigen obtained from saliva showed clinical and histologic changes identical with those seen in nodular vasculitis.

The management of diffuse progressive scleroderma has always been difficult. Evans[54] reports eleven patients who had undergone sympathectomy and were treated with relaxin (Releasin), a polypeptide-like hormone obtained from the ovaries of pregnant sows. There were nine women and two men in the series and all had undergone sympathectomy previously. In addition, patients were primed with diethylstilbestrol in doses of 1 mg daily, which was continued throughout therapy of seven to twenty-three months' duration. Relaxin helps to loosen the skin of patients with scleroderma. Improvement of dysphagia was noted in four of nine patients with esophageal scleroderma. Variable improvement was noted in pulmonary involvement and cutaneous ulcerations. One patient died of an anaphylactoid reaction after intravenous administration of relaxin.

In ten years, seventeen patients with periarteritis nodosa were admitted to the Rigshospitalet in Copenhagen, as reported by Bro-Rasmussen.[30] Of nine patients in whom the diagnosis was made prior to death, seven lived from six months to nine years after the diagnosis was made. This disease should be considered in patients with unusual combinations of symptoms and in vague progressive cases, with fever, muscular asthenia and weight loss. The diagnosis is supported by data of allergic manifestations, increased sedimentation rate, hypergammaglobulinemia, transient electrocardiographic changes and transient roentgenologic pulmonary changes. Only skin and muscle biopsies afford certain diagnosis. There is a tendency to remission in most cases in which the viscera are not involved, but the prognosis is unfavorable. Steroid therapy has been useful in suppressing symptoms and prolonging life.

Strauss[200] reported the case of a thirty-nine-year-old housewife who complained of intermittent appearance of reddish spots on her legs for the preceding year. Subsequently it was determined that she had purpura hyperglobulinemia of Waldenström since in addition to the purpura, analysis of serum proteins revealed consistently abnormal findings. There

were no cryoglobulins and no macroglobulins. It was thought that the syndrome presented a sensitivity to an insecticide for when she avoided this agent, she became free of purpura and abdominal pain. On two subsequent occasions within one hour of isolated exposures to the original insecticide, she had a fresh crop of purpuric lesions and some pain in the hip. This condition must be differentiated from cryoglobulinemia which is manifested at times by abdominal pain and some petechiae on the lower extremities. Urticaria, bullae and necrotic ulcers, the provocation of symptoms by cold and the presence of cold precipitins in the serum with normal globulin levels are distinguishing features. In macroglobulinemia of Waldenström, fatigue and anemia are more pronounced, lymphadenopathy is common, and bleeding occurs from mucous membranes and into the retina. Other conditions which need differentiating are Schönlein-Henoch purpura and the group of progressive pigmentary dermatoses of Schamberg and Majocchi. Purpura hyperglobulinemia seems to be a heterogeneous group of disorders.

An eighty-five-year old man with idiopathic cryoglobulinemia and cold agglutinins is described by Gaddy and Powell.[63] He showed signs of vascular damage of the Raynaud's type with cyanosis of the fingers which at times looked gangrenous. Weakness, stupor and aphasia became progressive and the patient died. Alteration of the globulins was suspected when routine blood examinations were performed. Immediate clotting in the syringe was noted. Cold precipitable globulins and high titers of cold agglutinins were found in this patient. These findings are rarely associated. In essential cryoglobulinemia, a small amount may be asymptomatic. It is associated with some cases of urticaria, Raynaud's, acrocyanosis, gangrene and necrosis. Visceral manifestations may be represented by cerebral purpura and retinal vein thrombosis. Secondary cryoglobulinemia is associated with neoplastic diseases, collagen diseases (lupus erythematosus and periarteritis nodosa), infectious diseases such as subacute bacterial endocarditis, coronary artery disease and cirrhosis of the liver.

Using guinea pigs, cats and rats, Nagy[134] and others conclude that Atabrine (quinacrine) has an antihistaminic action which is not explained by an increase of histaminase in the tissues of treated animals. All animals showed considerable hypertrophy of the adrenal cortex, and the suggestion is made that increased production of corticosteroids plays a part in the mechanism of the anti-inflammatory effect of quinacrine. Hydrocortisone hemisuccinate tablets were used as treatment by Truelove and Morris-Owen[209] in fifty-two patients suffering from aphthous ulceration of the mouth. The dose of four tablets a day was equivalent to 10 mg of hydrocortisone. No controls were used. Improvement was noted.

The question of whether allergic skin responses can be abolished under hypnosis was studied by Mason and Black.[114] Hypnosis was successful in preventing recurrence of hay fever and asthma in a woman twenty-seven years of age. At various intervals the patient was skin tested after each

treatment, and it was noted that sensitivity reactions gradually diminished on the arm. Responses were obtainable, however, on the leg at sites where the patient had never been previously tested. The leg reactions could also be abolished by specific suggestion. The reviewer notes that there is considerable difference of opinion about inhibition of allergic reactions by hypnosis. Children and babies can sometimes be tested with allergens while they are asleep and the results are practically the same asleep or awake. Of course, one could say that in hypnosis a different process holds.

Intermittent hydrarthrosis has been known for many years. Ensign and Sigler[52] discuss the disorder and consider some examples in their experience. The condition is sometimes the joint equivalent of Quincke's edema and may be associated with erythema, and angioedema of various parts at the same time. Recurrences are the rule. The authors conclude that the etiology of intermittent hydrarthrosis is not clear, yet the reviewer has seen this condition associated with patients of atopic background and others who were relieved successfully following allergic investigation.

More than eighty patients who had experienced serious allergic reactions to bee and wasp stings were studied by Mueller.[132] Exquisite sensitivity may be shown by patients who have had systemic reactions to stings of bees and wasps and great caution should be exercised in testing, treating, or both, these patients with extracts of insects. Patients with a positive family or personal history of allergy are more likely to have a severe sting reaction and the skin sensitivity may be demonstrated at higher dilutions. Multiple skin sensitivity was present in 85 per cent of the patients. Patients tested within ten days of the sting reaction had little skin sensitivity, suggesting a refractory state. Serial dilutions in skin testing helped in determining the proper level for starting polyvalent extract treatment. Without this, a level of 1 to 100 million should be the starting point. In response to a question regarding edema from insect bites, the consultant[153] states that the relief of edema in a sensitive reactor can be produced with any active antihistamine in adequate dosage. In cases of severe edema, corticosteroids may be required for control. Commercial extracts of mosquitoes are available for attempts at hyposensitization. Diethyl toluamide is recommended as a repellent. The reviewer notes that a preparation called "Off" is a pleasant, effective insect repellent.

Pacy[140] reports a papular and vesicular skin eruption in five men after massive exposure to a certain type of jellyfish (Aurelia). The contact with this particular genus is not immediately noted by patients. Stings of the larger jellyfish family are usually noted immediately, are painful and are probably on a toxic basis. In the reviewer's experience, patients with an atopic background usually report a much more violent reaction associated with urticaria and erythema multiforme-like lesions.

Bloom[23] and others report two cases of pyoderma gangrenosum associated with hypogammaglobulinemia. Improvement occurred in both on the administration of weekly injections of gamma globulin. Probably

the best management is the combination of steroids plus gamma globulin. In a similar fashion, nineteen cases of pyoderma gangrenosum were studied by Perry and Brunsting.[143] Chronic ulcerative colitis was present in eleven patients and six of the nineteen had other gastrointestinal disorders while two gave no clinical evidence of chronic ulcerative colitis. Arthritis frequently was an accompanying process. The reviewer notes that the mechanism and pathogenesis of pyoderma gangrenosum are not understood. The pathologic picture is not clear cut for any single process. Vascular allergy, Schwartzman reactions and auto-immune disease are likely possibilities. Ulcerative colitis is considered by some allergists as an allergic disorder. The relationship of cutaneous and gastrointestinal disorders was reviewed by Beerman and Greenbaum.[12] Associated with ulcerative colitis, one may see aphthae, urticaria, petechiae, pigmentary disturbances, angiitis and pyoderma gangrenosum—and, adds the reviewer, chronic, recurrent erythema nodosum.

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INDUCTION, DEDUCTION, AND HYPOTHESES

Hypotheses are more often than not inductively discovered, but they are not inductive by nature. Induction in this connection is the choosing of axioms for deductive purposes. A hypothesis is a proposition proposed for consideration, and as such it is neither inductive nor deductive. Induction refers to the manner in which a proposition is suggested by data disclosed to experience; deduction refers to the manner in which a proposition fits into a scheme of propositions. Thus there is no such thing as a hypothesis inductively or deductively discovered. Although the discovery of hypotheses calls upon the rarest of human faculties, imagination, and the presence of a hypothesis of some sort is the 'sine qua non' of the scientific method, it remains true that hypotheses are intended to fit eventually into a deductive scheme or else to be abandoned as worthless.—JAMES K. FEIBLEMAN, The Role of Hypotheses in the Scientific Method, in *Perspectives in Biology and Medicine*—Spring, 1959.

Papers of Interest

Sullivan, T. J., and Farber, E. M.: The problem of hand eczema. Postgrad. Med., 25:243-254 (March) 1959.
Eczematous lesions of the hands are grouped into 10 categories: namely, contact, infectious, and mycotic dermatitis, "Id" eruptions, nummular eczema, pompholyx, atopic dermatitis, food allergies and inhalant allergies, and miscellaneous eczematous dermatoses of the hands. Skin tests are considered of little value and hyposensitization regimens doubtful in their effect.

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In Memoriam

BERNARD GELFAND EFRON, M.D., F.A.C.A.

Bernard Gelfand Efron died February 16, 1960, of a cerebral vascular accident after a prolonged and incapacitating illness.

Born November 22, 1902, he received his formal education in the New York State Public Schools, Mt. Vernon College, The University of Maryland and Tulane University School of Medicine.

Although his close friends were well aware of his acuity, few knew that he was self-educated in the high school curriculum as well as in bio-statistics. His proficiency in the latter subject earned for him acceptance as an expert in Societies dedicated to this esoteric science. All of his studies were conducted by a well organized scientific approach; his conclusions only reached after statistical analysis of data. He had no tolerance for conjecture in scientific publication, for validation of anecdote, for plausibility as a substitute for proof. He was sometimes painfully articulate with transgressors.

He will be best remembered for a method of purification of house dust extract (Boatner, C. H., B. G. Efron and R. I. Dorfman: *Preparation of Purified House Dust Extracts,* Science, 91:389, 1940). However, one of his major contributions was the demonstration of the unitarian and specific nature of this antigen by comparative skin tests with extracts prepared from multiple sources. He also was one of the first to employ the statistical method for determining the diagnostic efficiency of extracts.

Excellent monographs on these subjects were published in Derbes and Engelhardt *Treatment of Bronchial Asthma* "The House Dust Factor," and for The International Correspondence Club of Allergy, "Biologic Analysis in Allergy." The latter publication is a classic demonstration of the application of the statistical method to skin test data.

Bernie Efron was an indefatigable worker. He was always to be found, nights, Sundays, holidays, working in his laboratory. He kept detailed notes of all his experiments. Allergy lost in him one of its keenest and most colorful students.

He is survived by his widow, Inez Frederick Efron; a daughter, Mrs. Norman Black of Houston, Texas; two brothers, Jack and Max Efron, and a sister, Miss Clara Efron.

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